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HISTORY OF THE DEVELOPMENT OF PURIFIED PROTEIN DERIVATIVE TUBERCULIN[1,2]

FLORENCE B. SEIBERT

A request has been made for a short résumé of the methods of approach and the results that have led to the development of the Purified Protein Derivative of tuberculin. Much of the work to be reviewed was undertaken as supplementary to work reported in the literature, especially where it was desirable to confirm or reinvestigate a conclusion. No references will be given to the literature in this review, since they have been listed adequately in various reviews and also in the papers on the individual phases of the work. A general survey relating these investigations to previous work is in press in *Bacteriological Reviews*.

The experimental work to which reference is here made will therefore be only that which has been carried out under grants from the Committee on Medical Research of the National Tuberculosis Association in the laboratory of the author, with a large number of collaborators, chief among whom was Dr. Esmond R. Long. No attempt will be made to give details concerning any procedure, since they can be more accurately and satisfactorily obtained from the individual papers.

At the outset a most vital precedent for the entire research was established, namely, the use of a synthetic medium for growing the bacilli. The medium (Long's) adopted was one which contained no protein and only pure chemicals, such as asparagine, ammonium citrate, glycerol and inorganic salts. On this medium the bacilli grew well and produced a filtrate which was highly potent as a tuberculin.

The first question, whether the active principle is or is not protein, was considered from many angles and a summary of the results leading to the conclusion that it is protein, is given below. It will indicate the nature of experimentation used in the studies.

1: When protein appeared in the culture medium, there was also tuberculin activity in the medium.

[1] From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, Pennsylvania.

[2] Aided by grants from the Committee on Medical Research of the National Tuberculosis Association.

2: When the protein was removed from such culture medium by protein precipitants, the tuberculin activity was also removed.
3: The nitrogen content of the purified precipitates paralleled its tuberculin potency.
4: The active material could be held back by thick dialysis membranes, and consequently could be concentrated greatly and freed of all small molecules by ultrafiltration. When the dialysis membranes were thinner, protein precipitable by trichloracetic acid was found in the ultrafiltrates, and there was also tuberculin activity in these filtrates. Otherwise, there was never more than a trace of potency.
5: Pepsin and trypsin destroyed the potency simultaneously with the breakdown of the protein molecule.
6: The active protein could be crystallized by the usual method used for crystallizing the protein egg albumin and the potency was shown to increase during fourteen recrystallizations.
7: The active principle behaved like a protein in physico-chemical procedures, including diffusion, high speed centrifuge sedimentation and electrophoresis, although it was evident that protein molecules of different molecular sizes were active.

There is now no question that the activity accompanies protein, although, as noted, proteins of different molecular sizes may be potent. An explanation indicating why activity may be expected in molecules of varying size will help to bring into accord many of the apparently discrepant opinions in the literature.

After it became obvious that the active material is protein, the next step was its isolation in pure form. At first, acetic acid was used as a precipitant and in the first experiments an attempt was made to cause precipitation at the isoelectric point, that is, that degree of acidity at which the substance was least soluble. However, it was soon found that such precipitation did not throw out the active material quantitatively, nor was the product so obtained as potent as that obtained in other ways.

Saturation with ammonium sulfate did precipitate the active principle quantitatively from the culture filtrate from which the live bacilli had been filtered, and even half saturation caused precipitation of most of the active material. The latter product was known as TPA, meaning "Tuberculin Protein Ammonium-sulfate Precipitated."

A more convenient method was found to be precipitation with trichloracetic acid. By this method the active principle was precipitated quantitatively from the culture medium filtrate, and, moreover, the

product could be reproduced as to analyses and potency. It was called TPT, meaning "Tuberculin Protein Trichloracetic Acid Precipitated," and was used in a great many investigations.

At that time, 1931–1932, the biological reactions of the TPA and TPT were investigated and the significant fact was noted that they were highly antigenic, that is, capable of eliciting precipitins, of producing typical anaphylaxis, and even of inducing typical Arthus reactions, when large amounts were repeatedly injected into normal guinea pigs or rabbits. These results were more conclusive than others previously obtained with bacillary extracts, since now there were available quantities of the purified fraction which could be made up into concentrated solutions of any desired strength.

It seemed advisable, therefore, to try to obtain a fraction with less antigenicity because of the possibility of eliciting false positive reactions due to sensitization with these highly antigenic preparations. Koch's Old Tuberculin might be a source of such material. However, since Old Tuberculin, even the modified variety made in synthetic medium instead of in glycerol broth, contains so much and so many impurities, it is not possible to make direct antigenic tests with it. For example, 1 cc. of a potent Old Tuberculin contains only about 10 mg. of the specific active material in approximately 300 mg. of organic and inorganic substance, and too much toxicity would be caused by the impurities present if one injected repeatedly 10 mg. (or 1 cc.) of the material, which is the amount used for eliciting an Arthus reaction with any protein.

A concentrated filtrate from cultures of tubercle bacilli grown on synthetic medium, essentially Old Tuberculin, except for the use of synthetic medium rather than of glycerol broth, can easily be freed of the excess salts and glycerol present by means of ultrafiltration, but even following this, about 50 per cent of the residue consisted of carbohydrate. Thus, further purification was necessary and it was found that precipitation of the ultrafiltered product with trichloracetic acid, removal of the acid with ether and simultaneous drying with the ether yielded a potent product, stable in its potency for years, and of the same degree of purity as the TPT, but far less sensitizing. This product was called the Purified Protein Derivative Tuberculin. It did not precipitate antiserum, nor produce a typical Arthus reaction when repeatedly injected intracutaneously in large amounts. Some oedema was produced, but the induration and necrosis of the typical Arthus reaction were lacking. However, when it was adsorbed to aluminum hydroxide or charcoal, it then did become

antigenic and did stimulate the production of precipitins, resembling a haptene.

This product proved to be very satisfactory for skin testing. It was, therefore, put up in quantitative tablet form, so that the addition of a specified amount of diluent to each tablet would give a solution already diluted for use as first or second intracutaneous dose. On the basis of extensive trial the first dose was chosen as 0.000,02 mg. and the second dose as 0.005 mg. The product has been used widely in tuberculin testing programs in this country and abroad.

This Purified Protein Derivative Tuberculin is practically nonantigenic and, in addition, in physico-chemical experiments it proved to be a comparatively small molecule, while the fractions made from the unheated tuberculin were larger molecules and were antigenic. Therefore, the idea was conceived that there may be a unit tuberculin protein molecule containing active groups responsible for the tuberculin activity. This unit by itself is not completely antigenic, but when two or more of these units are aggregated a molecule is produced, which is antigenic. The idea of a unit molecule and association of units is analogous to the conception of Professor Svedberg, concerning most proteins studied by him and his associates. He postulated the smallest protein unit molecule to be about 17,000 in molecular weight and actually all proteins studied have molecular weights which are multiples of this unit weight, including substances with weights 2, 4, 8, 16, 24, 48, 96, 192, 384 and 576 times this figure. Certain proteins, by association or dissociation, can exist as several different sizes, according to the environmental conditions.

It was decided that it would be worth while to determine whether the tuberculin protein might fit into the system expressed above. The importance of such an organization or system of molecules in understanding the nature of the tuberculin reaction cannot be overestimated. Furthermore, from the standpoint of general immunology or protein chemistry, no more ideal substance could be found for such a study, since few biologically active protein molecules have shown such remarkable stability in potency.

Therefore, an extensive study was made in Professor Svedberg's laboratory on representative tuberculin protein molecules, among which were the TPA, the most antigenic, and the Purified Protein Derivative, the least antigenic molecule. Physico-chemical analyses indicated that both products were chemically heterogeneous and required further purification before accurate molecular weights could be found. When this

purification was made the antigenic molecule was found to have a molecular weight of about 32,000, and the one isolated from the Purified Protein Derivative a weight of 17,000 to 18,000. Thus, the original idea appeared to be confirmed, but other complicating factors have since appeared.

In the meanwhile, while all the Purified Protein Derivative preparations made in our own laboratory seemed to have equal potency, those made in some other laboratories proved to be weaker. The reason for this had to be determined, especially in view of the fact that there came at this time to the National Tuberculosis Association a request for the preparation of a very large quantity of Purified Protein Derivative to be used as an official standard. Furthermore, during the more illuminating studies made possible by the refined physico-chemical and analytical methods recently available, it became apparent that it might be possible to produce by a simple method, as would be necessary for large scale production, a potent preparation of much greater chemical purity than heretofore. It was possible that chemical denaturation, to which purified proteins are peculiarly liable, was a cause of the variation in potency.

It seemed probable that less denaturation would result from (*1*) carrying out the entire procedure in the cold room, at 4 to 5°C., (*2*) using less heat, that is, by not evaporating on the steam bath, (*3*) using a weaker acid than 10 per cent trichloracetic acid for precipitation, and (*4*) obtaining the final product in dry form by the lyophile process, rather than by drying with ether or simply *in vacuo*.

Furthermore, through spectrographic, electrophoretic and analytical methods, it became evident that the original Purified Protein Derivative product contained more of the impurities, nucleic acid and polysaccharide, than one desires in a purified product. Recent studies in the Tiselius electrophoresis apparatus showed that the nucleic acid and protein readily separated and traveled as separate components at a reaction more alkaline than pH 5.0, whereas on the more acid side they migrated as a single component. Thus, if the precipitation could be made on the alkaline side rather than by acid, as was usually the case, a product with less nucleic acid should be expected.

In view of all these considerations, modifications were introduced in the original method for making the Purified Protein Derivative. The greater part of a year was utilized in the production of the large lot for an official standard, which was prepared with the collaboration of Mr. John Glenn at the Sharp and Dohme Laboratories. The proposed changes in

the method of preparation were tested in pilot experiments while the larger quantity of tuberculin was concentrating on the ultrafilters. The resulting products were analyzed and tested for potency and proved to be far more pure chemically and also twice as potent biologically as previous preparations, indicating that there was less denaturation.

Therefore, the large lot of Purified Protein Derivative was made by the modified procedure, including precipitation by half saturation with ammonium sulfate at pH 7.0, use of ice box temperature throughout the entire procedure, elimination of the evaporation on the steam bath and final drying from the frozen state. The exact details of the process can be found in the following paper. Approximately 3,500 cultures of human type tubercle bacilli were used, and a final yield of 107 g. of Purified Protein Derivative was obtained.

The product is being thoroughly investigated and it is hoped that even much more can be done than has so far been done. The results to date are as follows. The dried product is almost colorless, easily soluble in water and contains only 1.2 per cent nucleic acid and 5.9 per cent polysaccharide. It is twice as potent as our previous standard, that is, 0.000,01 mg. elicits as intense reactions in sensitive patients as 0.000,02 mg. of the previous product.

But the study is not yet finished, for it has proved to be somewhat more antigenic in producing the Arthus reaction than our previous Purified Protein Derivative, although less so than the unheated TPA. Repeated injections with small amounts, comparable to ten times our usual second dose, however, do not lead to significant sensitization in guinea pigs. Precipitins are also found in the sera of the sensitized rabbits and these precipitins show a certain degree of specificity different from the TPA.

This is all very interesting in view of the fact that the molecular weight has proved to be only about 10,500, that is, apparently smaller than the previous Purified Protein Derivative molecule. The sedimentation and diffusion curves show some heterogeneity and the electrophoretic pattern shows the presence of two mobile components. Attempts are being made to separate these two components. It is hoped that similar studies can be made with the unheated tuberculin for comparison.

In view of the fact that this Purified Protein Derivative has so low a molecular weight and still has the ability to elicit precipitins, it is possible that the size of the molecule is not as important a factor in the antigenicity as previously thought. It would seem rather that the po-

tency may be inherent in some part of the protein molecule and the antigenicity in some other part of the same or different molecule. The masking of either group would cause a loss in the respective potency. The exact relationship between these two properties is still not entirely clear.

The problem, however, can now be considered to be markedly limited, for now we have a highly potent molecule, which is practically free of nucleic acid and polysaccharide, so that one need no longer consider the active principle to be a nucleoprotein or a mucoprotein. On the other hand, the potent protein fraction still does not fulfil all the requirements of the most exacting modern physico-chemical methods for a homogeneous molecule. There still seems to be some contamination of the specific protein molecule with other protein. Whether it is different protein or some of the same protein in different combination or denatured is still not clear. From the practical standpoint this may not be important, but from the theoretical standpoint, in broadening our understanding of the nature of the tuberculin reaction, it will be important to pursue the problem further. The goal may not be so far away, since one product has been prepared which seems to contain very little of the contaminating fraction, without recognizable change in tuberculin potency.

All of the substances mentioned are to be found in Old Tuberculin, and, when one realizes the great complexity of such a mixture, it becomes clear that it is unreasonable to expect too close correspondence in the results obtained by its use.

Recently, it has been found that certain of these highly purified fractions, as well as being more potent per unit, give a larger percentage of reactors to the second dose strength intracutaneous test than previous preparations. The same thing was true with certain preparations of Old Tuberculin. The explanation of this fact is not yet clear, but is being intensively investigated. A corresponding increase in percentage of reactors to the first dose has not been found.

Much work is in progress to locate the limit of the dosage which will detect all those individuals with clinically significant disease, and then another dose which will detect those of epidemiological significance as well. From the data on hand, it would seem that the 0.000,02 mg. originally chosen for the first dose fulfils, at least within a few per cent, the former requirement. A slightly larger dose (0.0001 mg.) may detect even the few additional persons. It is quite clear, however, that the

usual second dose is larger than is necessary, and perhaps need not be used for this purpose.

The proper final dosage for epidemiological studies is not as yet so easily prescribed because a great many complicating factors must be considered. Questions such as a cross sensitization to organisms or substances other than the tubercle bacillus or its products, which may vary in different localities, a nonspecific irritability in certain persons and the degree of sensitization of different people, as well as personal differences in the interpretation of small reactions, must be considered. More work must be done before a clear distinction can be made between the truly specific and the nonspecific reactions to the larger dosage.

TUBERCULIN PURIFIED PROTEIN DERIVATIVE[1]

Preparation and Analyses of a Large Quantity for Standard

FLORENCE B. SEIBERT AND JOHN T. GLENN

The object of preparing this single large lot of Purified Protein Derivative was to secure a product of the highest degree of purity and potency and in amount sufficient for deposit as an official standard tuberculin. The method used was a modification of the original method published in 1934 (1). It includes a number of changes introduced to prevent denaturation of the specific protein responsible for the tuberculin reaction. For example, the procedures of concentration by ultrafiltration and purification were carried out entirely at low temperature, 5–6°C. The period of heating was limited to the heating in the Arnold sterilizer and there was no concentration on the steam bath. In order to secure a colorless product Long's synthetic medium was substituted for the Dorset culture medium originally used. The difference in the composition of the two media lay only in the quantity of some of the constituents, except for glucose, of which there was none in Long's medium. The reaction of the solution was kept at a pH of 7 to 7.4 throughout the entire process, and the precipitations were made at this pH. This latter modification was based upon electrophoretic studies (2), which showed that at reactions more alkaline than pH 5.0 the nucleic acid readily separated from the protein and migrated with a much greater mobility, whereas on the acid side of pH 5.0 the two substances migrated as a single substance. Some of these modifications had already been adopted by Jensen and his associates (3).

The method finally adopted was established through a number of pilot determinations, made while the tuberculin filtrate was concentrating. For example, two small aliquots, taken from the concentrating tuberculin, were precipitated by means of 2 per cent trichloracetic acid, four or five times, as indicated in table 1. The final precipitates were put into solution, neutralized with sodium hydroxide and washed free of

[1] From the Henry Phipps Institute of the University of Pennsylvania, Philadelphia, and the Mulford Biological Laboratories, Sharp and Dohme, Glenolden, Pennsylvania.

sodium trichloracetate on the ultrafilter, filtered through the Seitz pad and analyzed. They were designated as IIIa and IIIb in the table.

TABLE 1

Analyses

PURIFIED PROTEIN DERIVATIVE PREPARATION	TOTAL VOLUME OF SOLUTION USED	NUMBER OF TIMES PRECIPITATED	PROTEIN	NUCLEIC ACID	POLYSACCHARIDE
	cc.		*per cent*	*per cent*	*per cent*
IIIa	75	5	46.9	25.2	27.9
IIIb	20	4	49.2	27.2	23.6
IIIa2	35	3	93.7	0.8	5.6
49609	4,175	5	96.0	1.7	2.9
Standard	11,900	8	92.9	1.2	5.9

TABLE 2

Skin tests on pilot lots in dispensary clinic patients

PREPARATION OF PURIFIED PROTEIN DERIVATIVE	FIRST DOSE				SECOND DOSE			
	Dose	Number Tested	Number Positive	Average Dimensions of Reaction	Dose	Number Tested	Number Positive	Average Dimensions of Reactions
	mg.			*mm.*	*mg.*			*mm.*
20b (Original Standard)	0.000,02	157	62	16.4 x 15.4 x 2.0	0.005	84	42	20.4 x 17.9 x 2.1
71–2 (Present Standard)	0.000,01	157	62	17.1 x 16.0 x 1.9	0.0025	84	42	20.5 x 18.5 x 2.1
71–2	0.000,01	41	25	16.7 x 14.8 x 1.9	0.0025	13	10	18.6 x 16.6 x 2.3
IIIa2†	0.000,01	41	25	17.5 x 16.1 x 1.9	0.0025	13	10	19.0 x 18.0 x 2.3
71–2	0.000,01	8	7	15.4 x 13.8 x 1.9				
IIIb*	0.000,01	8	7	18.2 x 17.4 x 1.9				
71–2	0.000,01	79	59	17.1 x 15.7 x 1.9	0.0025	17	13	16.5 x 14.4 x 1.9
49609†	0.000,01	79	59	16.8 x 16.1 x 1.9	0.0025	17	13	16.8 x 15.9 x 1.9

* Preparation by precipitation with 2 per cent trichloracetic acid.

† Preparation by precipitation with neutral ammonium sulfate.

A third aliquot was precipitated three times by the addition of an equal volume of saturated ammonium sulfate, previously neutralized. The final precipitate was redissolved, washed free of ammonium sulfate, filtered through the Seitz filter and analyzed. It was designated as IIIa2 (table 1).

Another pilot experiment consisted of the production of 41 g. of Purified Protein Derivative by the method described for IIIa2, except that the tubercle bacilli were grown upon the Dorset synthetic medium. This preparation was designated as 49609 (table 1).

The analyses on these pilot lots showed that the products made by trichloracetic acid precipitation (IIIa and IIIb) contained a very high percentage of nucleic acid and polysaccharide, whereas those preparations made by neutral ammonium sulfate precipitation contained almost negligible traces of nucleic acid and very low amounts of polysaccharide. In fact, they were so pure that a standardization of the final solutions on the basis of their nitrogen content was justified.

The potency of the pilot lots proved to be excellent and in both cases equal to that of a product (71–2) used as a standard. This latter product was twice as potent as the previous standard (20b) prepared by the original method (see table 2).

On the basis of these results it was decided to use the method employed in making the IIIa pilot lot, for the preparation of the large standard lot, to be designated standard Purified Protein Derivative. The procedure was as follows:

PREPARATION OF THE STANDARD PURIFIED PROTEIN DERIVATIVE

The human type of tubercle bacillus, strain DT, obtained from the laboratories of the Bureau of Animal Industry, Washington, was seeded on veal infusion broth and when sufficiently grown, planted on Long's synthetic medium[2] in one litre bottles, containing about 200 cc. each. From 498 to 898 bottles of medium were planted at a time on six different occasions between June and September, 1939, as shown in table 3. In all there were 3,664 cultures and 733 litres of original medium. After incubation at 37.5°C. for from eight to ten weeks, the cultures were shaken and heated in the Arnold sterilizer for three hours. They were then taken into a large cold room where the temperature was maintained constantly at 4° to 5°C., and all subsequent manipulations were made

[2] Asparagine ..... 5 g.
Ammonium citrate 5
Potassium acid phosphate 3
Sodium carbonate (anhydrous) 3
Sodium chloride 2
Magnesium sulfate 1
Ferric ammonium citrate 0.05
Glycerol 50
Water to 1000

at this temperature. The bacilli were filtered from the culture liquid, first through a Buchner funnel and then through a Mandler candle. The total volume of filtrate was 530 litres.

It was believed originally that no preservative would be needed during the ultrafiltration at this low temperature, but it was soon found on the pilot lots that certain bacteria grew luxuriantly and that 2 cc. of toluol per litre were required to prevent their growth. Consequently three parts of tuberculin filtrate were mixed with one part phosphate buffer[3] at pH 7.3, containing 8 cc. toluol per litre, and this then was ultrafiltered. During the ultrafiltration, buffer containing 2 cc. toluol per litre was continuously added and in this way a concentration of 2 cc. toluol per litre was maintained constantly.

TABLE 3

Preparation of the Standard Purified Protein Derivative

LOT NUMBER	VOLUME OF ORIGINAL MEDIUM	VOLUME OF FINAL FILTRATE	FINAL VOLUME OF CONCENTRATED FILTRATE	TOTAL YIELD IN G. (BASED ON 2 PER CENT TRICHLORACETIC PRECIPITATION)	TOTAL GRAMS ISOLATED
	litres	*litres*	*cc.*		
1	112.6	86.8	1,200	16.2	
2	111.2	73.3	3,000	21.2	
3	99.6	68.8	1,000	9.8	
4	99.6	72.6	1,000	11.3	
5	175.6	130.4	3,700	40.0	
6	134.2	98.1	2,000	19.5	
Total.....	732.8	529.9	11,900	118.0	107

As in the original method, the filtered tuberculin was concentrated by means of ultrafiltration (1) on alundum shells impregnated with 11 per cent gun cotton, about 50 such filters being in use for each lot of filtrate. About 50 litres of the buffer were also added to each lot during the ultrafiltration, in order to wash out the medium constituents, and the concentration was continued until the solution contained about 0.7 to 1.3 per cent protein. This was easily determined by the precipitation test (4) with 2 per cent trichloracetic acid. A total of 11.9 litres of concentrated solution were obtained from the entire filtrate.

[3] The buffer was made as follows: 9.078 g. of KH_2PO_4 were dissolved in 1000 cc. distilled water; 23.87 g. of $Na_2HPO_4 \cdot 2H_{20}$ were dissolved in 1000 cc. distilled water. Two parts of the solution of the potassium salt were mixed with eight of the sodium salt, and the mixture was then diluted 1 to 5 with distilled water.

Each lot of concentrated filtrate was then filtered through a Mandler candle and lyophilized, in order to maintain it in sterile and stable form until all of the other lots were ready. The dried residues were almost white and very fluffy in appearance.

The lyophilized residues were finally redissolved in 4 litres of buffer and complete solution was obtained except for a slight turbidity, due probably to a small amount of denatured protein. This solution was distributed in twenty 400 cc. centrifuge bottles, 200 cc. to a bottle. To each was added 200 cc. saturated ammonium sulfate, previously neutralized to phenol red with solid disodium phosphate. The resultant ammonium sulfate precipitates were centrifuged, the supernatant solutions syphoned off and the precipitates dissolved in buffer. It was necessary, at this point, to redistribute the precipitate in 30 bottles (total 6 litres) instead of 20 bottles, in order to effect complete solution.

The clear solutions were again precipitated by half saturation with neutral ammonium sulfate, centrifuged and redissolved, and this was repeated six more times, making a total of eight precipitations. One bottle broke after the fifth precipitation and this was worked up separately. The seventh and eighth supernatants were colorless and water clear, and presumably as free as possible, as a result of the repeated precipitations, from the nucleic acid and polysaccharide. The final solution had somewhat more turbidity than existed at the beginning of the precipitations, probably due to denatured protein. It was filtered with difficulty through the Mandler filter, but the resulting solution was entirely clear, of a deep amber color, and had an opalescence such as is seen in strong protein solutions. The volume was 9,300 cc., and the 2 per cent trichloracetic acid test indicated that it contained about 113 g. of protein.

The solution was then ultrafiltered and washed free of sulfate with 67.3 litres buffer containing 2 cc. toluol per litre. The ultrafiltrate was practically colorless from the beginning and showed a trace of precipitate with 10 per cent trichloracetic acid only after the test solution stood for twenty-four hours, a result indicating very little loss of the protein. The concentrated solution was filtered through paper and the volume was 7,250 cc. It was then filtered through the Mandler candle and with the wash the final volume was about 7,850 cc.

A nitrogen determination on this sterile solution showed it to contain 13.3 mg. protein per cc., based on 16.3 per cent nitrogen for the protein (5). Thus there was a total yield of 104.4 g. Purified Protein Derivative.

The precipitate in the bottle which had broken in the centrifuge was purified separately in a similar manner and yielded 3.87 g. Purified Protein Derivative.

Vials were then filled with 3.75 cc., equivalent to 50 mg. Purified Protein Derivative, or 0.75 cc., equivalent to 10 mg. The product was dried by quick freezing of the sterile solutions and drying in the frozen state, that is, by the lyophile process. This method has been shown (6) to preserve the potency quantitatively, even in high dilutions such as are used for diagnostic testing. There was some loss in the filling of the vials and thus the final yield was 107 g. Purified Protein Derivative.

As noted in the description of the method used for preparing the Purified Protein Derivative, it was necessary to use toluol in order to prevent contamination of the tuberculin during concentration, even

TABLE 4

Skin tests in dispensary patients

PURIFIED PROTEIN DERIVATIVE PREPARATION	0.000,01 MG.			0.0025 MG.		
	Number Tested	Number Positive	Average Dimensions of Reaction	Number Tested	Number Positive	Average Dimensions of Reaction
			mm.			mm.
71-2	106	82	20.6 x 17.3 x 2.1	24	14	29.9 x 24.5 x 2.4
Standard	106	82	20.7 x 20.1 x 2.2	24	14	30.8 x 26.4 x 2.5
	0.000,02 MG.			0.005 MG.		
81	97	75	23.7 x 22.6 x 2.5	23	19	21.1 x 21.1 x 2.4
Standard	97	75	23.1 x 21.1 x 2.4	23	19	20.4 x 18.3 x 2.4

though the procedure was carried out at 4 to 5°C. This necessitated great vigilance and repeated filtrations through the Mandler candle and thus added greatly to the labor involved. Therefore, a small lot of Purified Protein Derivative was prepared, in which every step in the preparation was identical with that used in the case of the Standard Purified Protein Derivative, except phenol was used as a preservative. After the culture was freed of bacilli by filtration through the Mandler candle, to every litre of filtrate was added 250 cc. of a phosphate buffer solution of μ 0.1 and containing 2.5 per cent phenol. This resulted in a final buffer concentration of μ 0.02, pH 7.3 and 0.5 per cent phenol with the tuberculin. Thus the concentration by ultrafiltration could be carried out more leisurely and with no danger of contamination. The final washing on the ultrafilters to remove ammonium sulfate was also

made in the presence of 0.5 per cent phenol. The final product (8) contained 0.35 per cent nucleic acid and 3.6 per cent polysaccharide, and proved to be equal in potency to the Standard Purified Protein Derivative, as seen in table 4. Therefore, it is safe and even advisable to use 0.5 per cent phenol as a preservative during the preparation of Purified Protein Derivative.

CHEMICAL AND PHYSICOCHEMICAL TESTS ON THE STANDARD PURIFIED PROTEIN DERIVATIVE AND PREPARATION 49609[4]

Analyses for nucleic acid by means of the diphenylamine reaction showed 1.2 per cent nucleic acid, and for polysaccharide by means of the

TABLE 5

Physico-chemical properties

PURIFIED PROTEIN DERIVATIVE PREPARATION	S_{20}	D_{20}	MOLECULAR WEIGHT	MOBILITY × 10^5 cm^2 $volt^{-1}$ sec^{-1}			
				$\mu = 0.1$		$\mu = 0.02$	
				Ascending	Descending	Ascending	Descending
				At pH 7.3			
Standard	0.76	8.80	8,200	−7.5, −4.3	−6.2, −3.7	−12.9, −9.6	−6.7, −2.6
	1.15		12,400				
	1.013		10,900				
49609	1.32	8.65	14,500	−7.6	−6.2	−12.9	−7.2, −2.97
				At pH 8.0			
Standard				−8.1, −4.5	−7.1, −3.0	−12.2, −9.9	−8.0, −2.5

carbazole test showed 5.9 per cent total polysaccharide (see table 1). This latter figure includes 4.7 per cent true tuberculin polysaccharide.

The results of physico-chemical studies are shown in table 5. The determinations of the sedimentation and diffusion constants were made by Dr. Janet McCarter and Mr. Dennis Watson with the use of the Svedberg ultracentrifuge and the Lamm diffusion cell, in the laboratory of Dr. J. W. Williams at the University of Wisconsin, to all of whom we express our appreciation. An average of the molecular weights, calculated from three determinations of S_{20}, gave 10,500. Thus the average molecular weight is smaller than the 15,000 to 18,000 found for the

[4] Work on the further purification of these fractions is in progress in collaboration with the laboratory of Professor Arne Tiselius, Upsala, Sweden.

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Purified Protein Derivative preparations made by the original method and studied previously (5). The sedimentation curves showed some heterogeneity. The corresponding curves for the Purified Protein Derivative 49609, which proved to have a molecular weight of about 14,500, were more homogeneous. Both curves, however, showed more homogeneity than did a Purified Protein Derivative made by the original method (see figure 1). The diffusion curves of the preparation 49609 almost coincided with the normal distribution curve, indicating a high

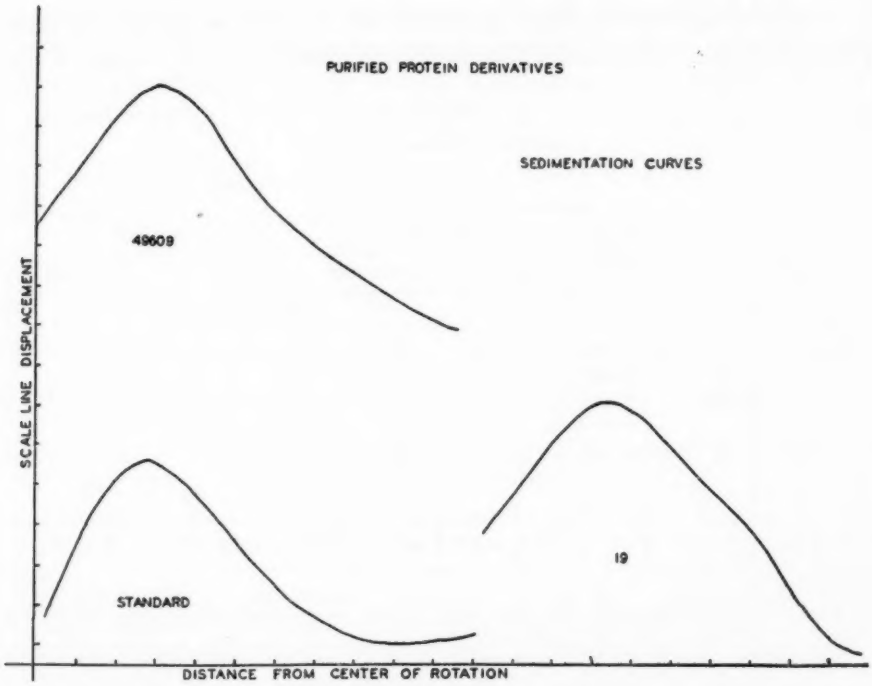

FIG. 1

degree of homogeneity, but this was not true for the curves of the Standard Purified Protein Derivative.

The electrophoretic mobilities, as determined in the Tiselius electrophoresis apparatus (7), were considerably different at the ascending boundaries in the two different buffer concentrations of $\mu = 0.1$ and $\mu = 0.02$, whereas at the descending boundaries they were more nearly alike (see table 5). Furthermore, identical mobilities were found for the fast components in the Standard Purified Protein Derivative and in the

ELECTROPHORETIC CURVES OF PURIFIED PROTEIN DERIVATIVES

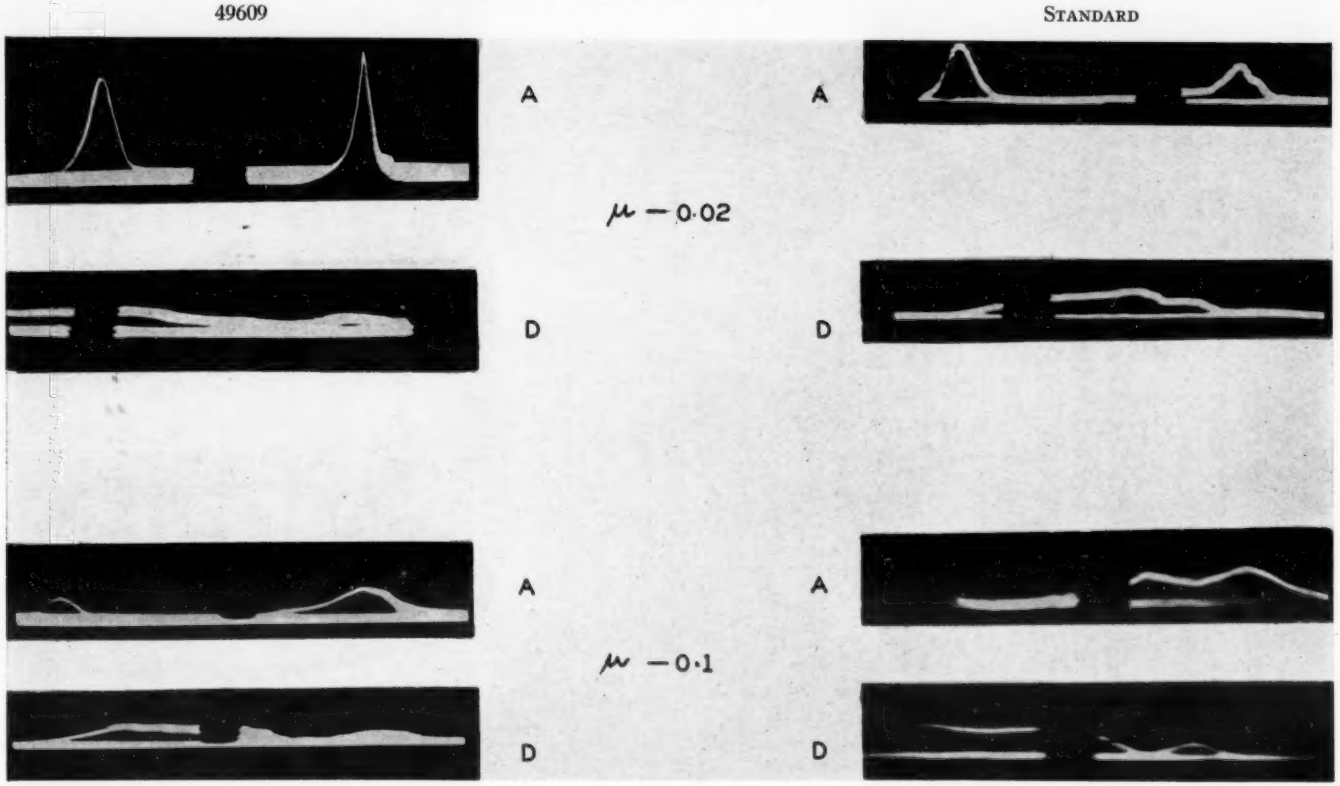

FIG. 2

Direction of migration of A →
Direction of migration of D ←

Purified Protein Derivative 49609 indicating that a similar component exists in the two preparations. Figure 2 shows the electrophoretic patterns obtained. It is clear that in both preparations sharper curves on the ascending side (A) were obtained in the buffer of lower concentration, $\mu = 0.02$. The curves on the left hand side of the ascending diagrams represent polysaccharide plus some anomalous (δ) boundary and those on the right are the migrating protein boundaries. In the case of the Standard Purified Protein Derivative, especially at $\mu = 0.1$, two mobile components appear, which do not separate into distinct boundaries, but appear to cling together, making the boundary broad and diffuse. Evidence of this tendency for the boundary to spread is also seen in the broad curve (A) for the mobile component in Purified Protein Derivative 49609 at $\mu = 0.1$. That there are two mobile components in Purified Protein Derivative 49609, in addition to the immobile one, is seen in the descending pattern, at $\mu = 0.02$, which is very diffuse.

All descending boundaries (D) spread out practically through two compartments. The mobility of the slower component is of the order found for the slower components associated as impurities with one type of polysaccharide isolated from the tuberculin filtrate (8). In the case of this polysaccharide there was evidence of a phenomenon of great tenacity between it and the nitrogenous impurities, some of which were protein, and it is possible that some of this same effect may be present in the case of the Standard Purified Protein Derivative. If such is the case, it would explain why 5.9 per cent polysaccharide was still present after eight precipitations and also why the electrophoretic curves appear to be so diffuse in spite of the fact that the product by analyses is purer than all previous preparations of Purified Protein Derivative. The product will be studied more extensively from this standpoint in the future.

The presence of a greater amount of this component with low mobility in the Standard Purified Protein Derivative than in the preparation 49609, as is evident from the electrophoretic diagrams, might also explain the fact that the sedimentation curves of the former preparation are less homogeneous. It is certain that more of the slow component is evident at the higher salt concentration, $\mu = 0.1$. Pedersen (9), and recently Longsworth, Cannan and MacInnes (10) have stated that there is greater association between components at low salt concentration, especially if one is carbohydrate.

BIOLOGICAL TESTS ON THE STANDARD PURIFIED PROTEIN DERIVATIVE AND PURIFIED PROTEIN DERIVATIVE 49609

Lethal tests in tuberculous guinea pigs showed that 2 out of 6 died in twenty-four hours following an intraperitoneal injection of 0.5 mg. of the Standard Purified Protein Derivative, and one out of 3 died following an injection of 1.0 mg. Autopsy revealed typical tuberculin death with congestion of the splanchnic area, including the adrenals, and fluid and mucus in the abdominal cavity.

Intracutaneous skin tests in human beings (table 4) indicated that the Standard Purified Protein Derivative gave reactions of equivalent size to the 71–2 preparation and was, therefore, twice as potent as the previous standard (see table 2 also).

A study was then made to determine how much sensitization could be brought about by repeated intracutaneous injections of large amounts (10 mg.) of the Standard Purified Protein Derivative.[5] It had been noted previously (11) that the Purified Protein Derivative gave comparatively smaller skin reactions following repeated injections than did the tuberculin protein fractions isolated from unheated filtrate and that these reactions lacked the induration and necrosis characteristic of the typical Arthus reaction elicited by the latter. Since the actual reactions obtained in this series had not been recorded previously they are noted in table 6. Comparisons, therefore, can be made with table 7, which records the reactions obtained by repeated injections of the Standard Purified Protein Derivative. It is clear that more sensitization occurred with the Standard Purified Protein Derivative than with the previous Purified Protein Derivative, but not as much as with the protein precipitated by ammonium sulphate (TPA) from unheated filtrate.

An effort was, therefore, made to determine whether significant sensitization might occur from repeated intracutaneous tests with small doses of the Standard Purified Protein Derivative, more nearly like the usual second dose in man. Ten times the usual second dose, or 0.05 mg., was used and table 8 shows that nine such injections in normal guinea pigs did not produce reactions of any significance. In view of the small reactions that did occur, as well as other recent studies suggesting a nonspecific nature of the second dose reactions, it is probable that very small and questionable reactions to the usual second dose should be discounted.

[5] This series of tests was made by Mr. Dennis Watson.

TABLE 6

FRACTION	10 MG. INJECTED ON	RABBIT # 227	RABBIT # 224	RABBIT # 2083
		Dimensions of reaction at twenty-four hours in mm.		
TPA (from unheated filtrate)	4/26	22 x 32 (pale, slight oedema)	37 x 50 (slight oedema)	40 x 45 (erythema, slight oedema)
	4/30	30 x 42 (light red, oedema)	40 x 42 (more oedema) (10 x 10 centre)	35 x 36 (oedema) (5 x 5 centre)
	5/3	48 x 50 (much oedema)	65 x 90 (much oedema)	25 x 60 (pale oedema)
	5/8	85 x 120 (much oedema)	112 x 125 (induration) (8 x 10 centre)	37 x 65 (oedema)
	5/11	80 x 90 (some induration) (7 x 7 centre)	60 x 90 (marked induration) (7 x 11 centre)	70 x 80 (some induration) (10 x 12 necrosis)
	5/21	95 x 100 (marked induration) (7 x 10 centre)	65 x 80 (marked induration) (9 x 9 necrosis)	80 x 110 (marked induration) (8 x 10 centre)
	6/1	73 x 88 (marked induration)	85 x 95 (marked induration) (15 x 15 centre)	
Reaction to 10 mg. Purified Protein Derivative at end of series of injections	6/4	95 x 110 (pale, some induration)	55 x 62 (some induration) (10 x 12 necrosis)	50 x 80 (marked induration)
		RABBIT # 144	RABBIT # 146	
Purified Protein Derivative	4/30—1st	16 x 29 (trace oedema)	17 x 22 (trace oedema)	
	6/1 —7th	38 x 40 (oedema)	35 x 45 (oedema)	
		RABBIT # 147	RABBIT # 148	
Purified Protein Derivative adsorbed to $Al(OH)_3$	4/30—1st	12 x 18 (trace oedema)	21 x 23 (trace oedema)	
	6/1 —7th	52 x 60 (induration) (15 x 19 centre)	45 x 55 (oedema)	

Another method for studying sensitization, that is, by means of the precipitin reaction, was also investigated. The 2 normal rabbits which had received the series of eleven intracutaneous injections of 10 mg. of the Standard Purified Protein Derivative were bled to death. Table 9 shows that their sera contained precipitins to the three antigens tested. This is contrary to results obtained previously (11) in which Purified Protein Derivative did not elicit precipitins of any significance. Some of these previous results are included in the table for comparison. However, when in the earlier studies Purified Protein Derivative had been

TABLE 7

Sensitization by repeated intracutaneous injections

STANDARD PURIFIED PROTEIN DERIVATIVE 10 MG. INJECTED ON	DIMENSIONS OF REACTION IN RABBIT # 689 IN MM.	DIMENSIONS OF REACTION IN RABBIT # 511 IN MM.
7/5	0 (slight erythema)	20 x 30 (erythema and oedema)
7/8	48 x 50 (some induration)	40 x 83 (erythema and oedema)
7/11	40 x 60 (erythema and oedema)	38 x 55 (induration)
7/15	50 x 70 (marked induration)	60 x 70 (induration)
7/19	50 x 60 (marked induration)	50 x 80 (induration)
7/22	50 x 50 (erythema and induration) (5 x 5 centre)	50 x 60 (induration)
7/23	50 x 50 (induration) (10 x 10 centre)	50 x 50 (induration) (5 x 5 necrosis)
8/2	40 x 50 (induration) (5 x 5 centre)	40 x 50 (induration) (5 x 5 centre)
8/12	40 x 40 (induration)	40 x 55 (induration)
8/19	40 x 50 (induration) (5 x 5 centre)	30 x 40 (induration)
8/26	40 x 50 (induration)	40 x 40 (induration)

adsorbed to aluminum hydroxide or charcoal and then injected, precipitins were obtained. It is to be noted that in these latter cases, as well as in the case of the antisera to the Standard Purified Protein Derivative, the highest titres were obtained with the homologous antigens. Likewise the highest titres to the TPA antisera were obtained with the TPA. Thus, there appears to be some specificity in the two molecules. The fact that the Standard Purified Protein Derivative is a much purer preparation than the previous Purified Protein Derivative as determined by chemical analyses, and that it is no larger in molecular weight but, in fact, even slightly smaller, suggests that the specificity observed may be due to the fact that certain groups are unmasked in the Standard Purified Protein Derivative or that there is less denaturation than in the

TABLE 8

Reactions to repeated intracutaneous tests of 0.05 mg. Standard Purified Protein Derivative—dimensions in mm.

NORMAL GUINEA PIG	TIME OF READING	10/15 0.005 MG.	10/22	11/4	11/7	11/11	11/14	11/18	12/4	12/9
	hours									
1	24	0	0	trace	10 x 10 x 1	7 x 5 x trace	7 x 8 x trace	4 x 4 x trace	trace	0
	48	0	0	0	?	0	trace	0	0	0
2	24	0	0	0	0	4 x 5 x trace	5 x 5 x trace	0	7 x 8 x 1	0
	48	0	0	0	0	0	0	0	0	0
3	24	0	6 x 7 x trace	6 x 9 x trace	8 x 9 x trace	12 x 13 x 1	4 x 5 x trace	8 x 9 x 1	4 x 4 x trace	8 x 9 x 1
	48	0	0	0	0	10 x 12 x 1	trace	4 x 4 x trace	trace	0
4	24	0	5 x 6 x trace	0	12 x 12 x 1	12 x 12 x 1	6 x 8 x 1	7 x 8 x 1	6 x 8 x 1	7 x 8 x 1
	48	0	0	0	0	4 x 5 x trace	4 x 5 x trace	trace	0	0
5	24	0	?(scratch)	8 x 9 x trace	7 x 10 x 1? (scratch)	7 x 9 x 1	0	9 x 10 x 1	9 x 10 x 1	9 x 9 x 1
	48	0	?(scratch)	0	4 x 5 x trace	4 x 6 x 1	0	3 x 4 x trace	0	0
6	24	0	0	8 x 10 x trace	10 x 12 x 1	6 x 8 x 1	4 x 5 x trace	8 x 8 x 1	0	0
	48	0	0	7 x 8 x trace	10 x 11 x trace	5 x 8 x trace	0	0	0	0

case of the previous Purified Protein Derivative. The greater potency of the Standard Purified Protein Derivative would, furthermore, support these suggestions.

The first possibility, that is, that certain reactive groups may be unmasked in the more highly purified product, was tested in the following manner. The impurities, namely, nucleic acid and the two types of polysaccharide mentioned above (8) which had been removed, may be suspected to be the substances capable of causing the masking effect.

TABLE 9

Precipitin titres

ANTISERA	ANTIGENS				
	Purified Protein Derivative 20	Standard Purified Protein Derivative	Purified Protein Derivative 49609	TPA	Polysaccharide (Tuberculin)
To Purified Protein Derivative 20	1: 400 0			1: 200 0	
To Purified Protein Derivative adsorbed to Al $(OH)_3$	1: 400,000 1: 400,000			1: 40,000 1:100,000	
To Purified Protein Derivative 20 adsorbed to charcoal	1: 400,000			1:400,000	
To Standard Purified Protein Derivative	1: 10,000	1: 70,000 1:100,000	1:100,000 1:100,000	1: 30,000 1: 20,000	
To TPA	0 1:1,000–4,000 1: 10,000 0			1:100,000 1:400,000 1:400,000 1:100,000	
To Whole Dead Tubercle Bacilli (Horse Antiserum #5807A)	1: 100,000	1: 40,000	1: 40,000	1: 70,000	1:15,000,000

Therefore, each of them, in highly purified form, was added to Purified Protein Derivative and then the precipitin tests were made, using these mixtures as antigens against one of the Standard Purified Protein Derivative antisera. No effect was noted on the precipitin titre in any case.

SUMMARY

A large quantity of Purified Protein Derivative Tuberculin was prepared to serve as a tuberculin standard.

Modifications in the original method of preparation were introduced, which yielded a product with much reduced amounts of nucleic acid (1.2 per cent) and polysaccharide (5.9 per cent) and a potency, as determined by the Mantoux test, twice that of the former Purified Protein Derivative. This product was made without the use of phenol, but it was shown that the use of 0.5 per cent during the preparation does not decrease the potency.

The final product was dried from the frozen state (lyophilized) and preserved in sterile form and *in vacuo*, which should insure its stability for an indefinite period of time.

Physico-chemical studies indicated that it had a molecular weight of about 10,500. The sedimentation curves showed some heterogeneity and electrophoretic diagrams also showed the presence of at least two mobile components, especially at the higher buffer concentration. Either the interaction between these components was increased at low buffer salt concentration or the formation of a second component was facilitated by increased salt concentration.

By repeated intracutaneous injections of large (10 mg.) amounts of the Standard Purified Protein Derivative into normal rabbits a certain degree of sensitization (Arthus reaction) was produced which was somewhat greater than that caused by the previous Purified Protein Derivative preparations and less than that caused by tuberculin protein precipitated with ammonium sulphate (TPA). However, repeated injections of small amounts of the Standard Purified Protein Derivative, namely, ten times the regular second dose used in the skin test, did not lead to significant sensitization in guinea pigs.

The sera of the rabbits sensitized to the Standard Purified Protein Derivative contained precipitins. There seemed to be a certain degree of specificity between the TPA and Purified Protein Derivative molecules.

We express our thanks to Dr. John Reichel for his encouragement support and active interest throughout this work.

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PULMONARY INSUFFICIENCY[1,2]

I. Discussion of a Physiological Classification and Presentation of Clinical Tests

ANDRE COURNAND AND DICKINSON W. RICHARDS, JR.

Pulmonary insufficiency has been analyzed, from the point of view of pathological physiology, in several excellent recent papers. Those by Knipping (1, 2, 3) and Anthony (4, 5) are perhaps outstanding. These investigators have gone into considerable detail in their descriptions of pulmonary insufficiency, with classification and division into a number of different forms.

For the purposes of clinical medicine, it has seemed to us that the simplest possible classification would probably be the most useful, and we believe that, in the existing state of knowledge, a simple and useful classification of pulmonary insufficiency can be made.

Pulmonary function can be divided broadly into two parts: *ventilatory*, the function concerned with movement of atmospheric air into and out of the lungs; and *respiratory*, the function concerned with (*a*) the diffusion of oxygen from alveolar spaces into the blood, providing adequate oxygenation of haemoglobin; and (*b*) the elimination of carbon dioxide from blood to alveolar air.

Thus the ventilatory aspect of pulmonary function is largely mechanical. The major symptom of ventilatory insufficiency is *dyspnoea*.

The respiratory aspect of pulmonary function is largely physicochemical. The major symptoms of respiratory insufficiency are those of anoxia, of which *cyanosis* is the most obvious.

PULMONARY INSUFFICIENCY

FORM	TYPE OF FUNCTION	SYMPTOMS
Ventilatory	Mechanical	Dyspnoea
Respiratory	Physicochemical	Anoxia (cyanosis, etc.)

It should be emphasized that the purpose of the above description is to provide a useful approach to the symptomatology of pulmonary (and

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[2] Under a grant from the Commonwealth Fund.

pulmono-circulatory) disease. It is not intended as an adequate analysis of all the complicated interrelations of pulmonary physiology. It is obvious, for example, that the ventilatory and respiratory mechanisms are at all times closely interrelated: ventilatory insufficiency, if sufficiently severe, will necessarily induce respiratory insufficiency; conversely, respiratory insufficiency will add to the stimulus of the respiratory centre and tend to increase ventilation.

Of particular importance is the place where the ventilatory and respiratory functions meet, namely the alveoli. Adequate pulmonary function demands not only the inhalation of proper volumes of air, but the distribution of this air to alveolar spaces that are being perfused with pulmonary blood; in other words, the *aeration* of the ultimate alveolo-capillary units. This phase we have included as a part of respiratory function.

Clinically, it is not uncommon to find cases of almost pure ventilatory insufficiency. Cases of purely respiratory insufficiency are also seen, but are rare. For the most part, however, this classification of pulmonary insufficiency will be found useful in evaluating the disability of each patient. Thus, most patients with physical disability due to chronic pulmonary disease will have some degree of ventilatory failure and also some degree of respiratory failure. A proper estimate of these two aspects may mean much in determining adequate therapy.

A still further complicating factor is cardiocirculatory failure. This also requires evaluation, as a part of the total dysfunction in any given case. As is well known, cardiac failure may manifest itself by strictly pulmonary symptoms, and pulmonary function itself may be badly compromised from purely circulatory causes.

Thus for practical purposes, four major categories of pulmonary insufficiency can be recognized:

I: Ventilatory insufficiency, or failure of the breathing mechanics to provide the required pulmonary ventilation without dyspnoea.
II: Respiratory insufficiency, or failure to maintain normal respiratory gas interchange between the alveoli and the pulmonary capillaries.
III: Combined ventilo-respiratory insufficiency.
IV: Combined cardio-pulmonary insufficiency of various types.

The object of this paper is to review the physiological principles which form the basis of this differentiation, to present a group of clinical tests used for the evaluation of pulmonary and circulatory function, and to

discuss some points of technique. In papers to follow, an attempt is made to estimate the effects on pulmono-circulatory function of various types of collapse therapy.

VENTILATORY INSUFFICIENCY

Ventilatory insufficiency results from decrease in ***maximum breathing capacity***, increase in ***breathing requirement***, or a combination of both.

A. *Maximum Breathing Capacity*

Maximum breathing capacity, often referred to as maximum ventilatory volume (6) (*Atemgrenzwert* of the German authors), measures the maximum volume of air that can be ventilated in unit time. Maximum breathing capacity expressed in liters per minute provides, we believe, a measurement better correlated with actual ventilatory function than the measurement of the maximum volume change of a single breath without regard to time (that is, the vital capacity). Decrease in maximum breathing capacity is brought about by restriction of, or obstruction to, air circulation. Maintenance of a large maximum breathing capacity is dependent upon the integrity of the following structures:

1: The chest bellows, the amplitude and speed of volume change of which is regulated by a highly integrated and coördinated neuromuscular system.
2: The tracheobronchial pulmonary airway.
3: The pulmonary tissue, considered here chiefly for its elastic properties.

Thus, limitation in maximum breathing capacity may occur (*1*) from abnormality of the chest wall or disturbance of the neuromuscular apparatus of breathing, as in advanced kyphoscoliosis or following diaphragmatic paralysis; or (*2*) from obstruction in the air passages, such as in asthma and obstructive emphysema; or (*3*) from limitation in pulmonary elasticity, such as in fibrosis or pulmonary congestion.

Four methods for estimating the maximum volume of air which can be ventilated per unit time have been described. Definitely contraindicated in our group of patients were methods requiring heavy exercise (7) or carbon dioxide rebreathing (8). The measurement of a *single* deep and rapid breath in relation to time, used by Gaubatz on a large scale in tuberculous patients (9), gives obviously too low values. The best method available for our purposes is that described originally by Hermannsen, which we have discussed recently (10). This consists essentially in having the subject (connected to a spirometer) perform his maximum ventilatory effort, allowing him to choose

his own rate and depth; and having this maximum ventilatory volume recorded graphically on a moving drum.

To determine the maximum breathing capacity by the voluntary method of Hermannsen is simple; it does not require prolonged effort nor special training; its results are reproducible. In normal subjects the values obtained are much larger than by measuring ventilation during heavy exercise, which in the largest series reported (7) averaged 80 liters in males and 50 liters in females. In the group of 20 normal males and 20 normal females tested by Hermannsen's method, which we previously reported (10), the mean values for maximum breathing capacity were respectively 154 liters per minute for males and 100 liters per minute for females. Although based on determinations in groups of limited numbers, these values, as further studies actually in progress indicate, seem to be quite representative. A much larger series and a less uniform population with regard to age, physical characteristics and state of training, will be required before one is permitted to calculate percentage ratio of normal in pathological cases. The relation between vital capacity and maximum ventilatory volume per minute has been emphasized by Peabody. If a high correlation exists, the simple measurement of the vital capacity should permit a prediction of the maximum breathing capacity. In our two groups of normal subjects, the coefficients of correlation were $r = +.489$ S.E. $\mp.17$ in males (P between .05 and .02), and $r = +.539$ S.E. $\mp.16$ in females (P between .02 and .01); although statistically significant,[3] they do not approach perfection sufficiently to permit such a prediction. That is, the vital capacity cannot be relied upon as a quantitative measure of ventilatory capacity.

B. *Breathing Requirement*

Breathing requirement is the actual volume of ventilation per minute in any given physical state. This volume, regulated by reflex stimula-

[3] The value assigned to P indicates the probability that the difference observed between two means, or the correlation between two measurements, is due merely to chance. The lower the value of P, the greater the significance of a difference or of a correlation. (*a*) To test the significance of a coefficient of correlation (r) in a small sample, table Va on page 174 of *Statistical Methods for Research Workers* by R. A. Fisher was used. (*b*) To test the significance of a difference between the means of two groups, the following calculation is made:

$$t = \frac{\text{difference of the 2 means}}{\text{standard error of the difference of means.}}$$

P is then read from the t value entered in the table prepared by "Student" for small samples (table, page 137 of *Statistical Methods for Research Workers* by R. A. Fisher).

tion of the respiratory centre, varies with the state of metabolism, posture, exertion, anoxia of blood and tissues, emotional and other nervous states.

In the group of cases which we are reporting, it was measured (*a*) with the subject supine under basal conditions; (*b*) during a standard exercise, consisting of stepping up and down a step 20 cm. high 30 times in one minute; and (*c*) during the period of recovery, limited to the five minutes following the cessation of exercise. This simple type of exercise is usually managed without undue fatigue, even by patients with considerable disability.

Quantitative measurements of ventilation in the three states of rest, exercise, and recovery, are secured by collecting expired air in a Tissot gasometer and

TABLE 1

*Ventilation and respiratory gas exchange in a control group at rest under basal conditions and during standard exercise**

	REST		EXERCISE	
	Mean	Standard deviation	Mean	Standard deviation
Ventilation, lit./min. per sq.m.B.S.†	3.20	±.65	9.70	±1.81
Carbon dioxide output				
cc./min. per sq.m.B.S.‡	101.9	±15.0	318.1	±73.3
cc./lit. ventilation	36.3	±5.8	37.2	±3.3
Oxygen intake				
cc./min. per sq.m.B.S.‡	132.0	±12.8	468.0	±73.7
cc./lit. ventilation	46.8	±7.1	54.8	±6.2
R.Q.	.776		.678	

* The control group consisted of 15 hospital patients without pulmonary or cardiocirculatory disease.

† Saturated gas at 37°C. and prevailing barometric pressure.

‡ Dry gas at 0°C. and 760 mm. Hg.

a Douglas bag. A special kymograph, electrically driven, records also the motion of the bell of the gasometer through an ink pen attached to the scale. Thus rate of respiration and volume of air ventilated during each of the five minutes of the recovery period can be easily read from the record. Basal ventilation is calculated from the average of two successive periods of ventilation of six minutes each, separated by a fifteen-minute interval of rest. During the performance of the exercise, the subject is connected to the Douglas bag; and at the end of the one-minute exercise period, while he resumes the recumbent position, the expired air is shunted to the Tissot gasometer through a three-way valve. All ventilatory volumes are measured as saturated gas, at 37°C. and prevailing pressure.

In table 1 are tabulated the mean values and standard deviations obtained in a control group of 15 hospital patients without pulmonary or

cardiocirculatory disease, to serve as a basis for comparison with patients suffering from chronic pulmonary disease.

C. *Breathing Reserve*

The *excess breathing capacity* beyond the *actual ventilation* in any given physical state is the *breathing reserve*. According to this conception, the maximum breathing capacity being in each subject a fixed value, the breathing reserve varies inversely with the breathing requirement, and for comparative purposes may be expressed in per cent of the maximum breathing capacity. Thus in a subject whose maximum breathing capacity = 150 liters per minute, and ventilation at rest = 5 liters per minute, the breathing reserve = 145 liters; and the ratio $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ at rest = 145/150 = 96.6 per cent. Similarly, in the same subject, if the ventilation during exercise = 25 liters per minute, the breathing reserve being 150 − 25 = 125 liters per minute, the ratio $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ during exercise = 125/150 = 83.3 per cent.

D. *Ratio* $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ *and Dyspnoea*

(*1*) In an analysis of 105 consecutive cases, the ratio $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ was calculated during each of the five minutes following the completion of the standard exercise previously described; and the relation was established between this ratio and the ventilatory level at which dyspnoea develops. In 37 cases of this group no dyspnoea was experienced. Averaging the ratio $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ observed in each of these 37 cases during the first minute of recovery, it is shown that the mean breathing reserve, then at its lowest, is still 73 per cent of the maximum breathing capacity. In the remaining 68 cases (chart 1), in which dyspnoea was present for varying lengths of time, the average ratios $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$, during the last minute preceding and the first minute following the cessation of dyspnoea, were respectively 63.2 and 71.5. Although the scattering of observations indicates that,

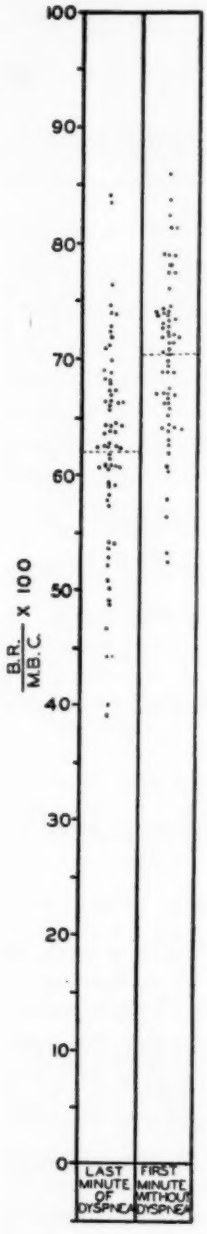

CHART 1

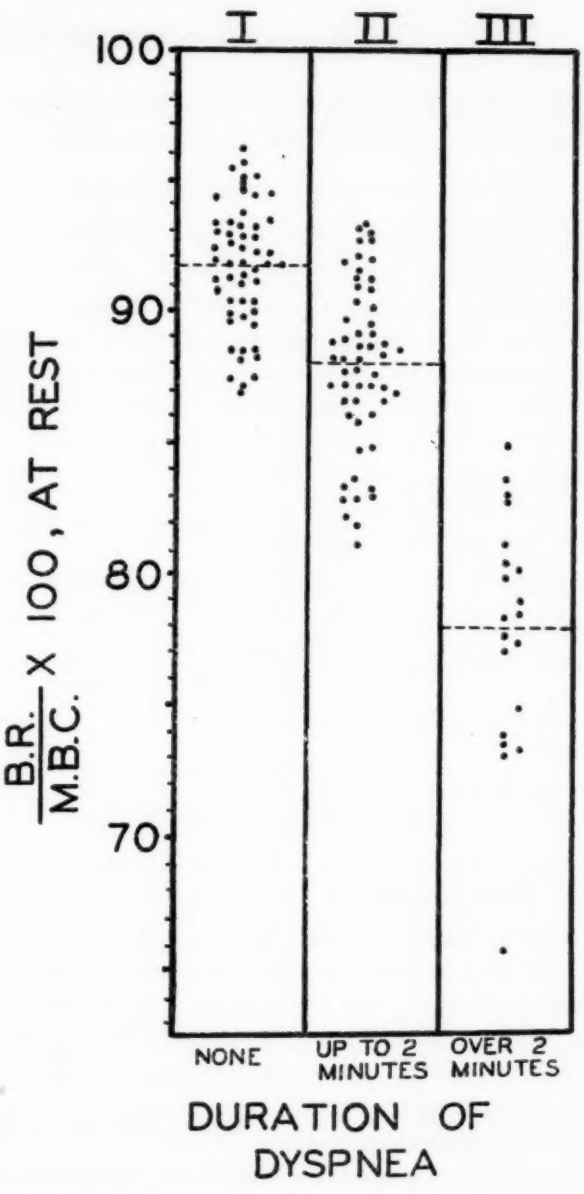

CHART 2

CHART 1. In each of 68 cases of chronic pulmonary disease manifesting the symptom of dyspnoea following the performance of a standard exercise, the ratios $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ are plotted separately in two columns: (1) on the left, during the last minute preceding the cessation of dyspnoea, (2) on the right, during the first minute following the cessation of dyspnoea. Mean values for the ratios are indicated by horizontal broken lines.

CHART 2. Ratio of $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ at rest in 129 cases of chronic pulmonary disease and its relation to the presence and duration of dyspnoea, observed during the recovery period following a standard exercise.

in a few instances, dyspnoea is still felt when the breathing reserve is 75 per cent of the maximum breathing capacity, it appears that the threshold of dyspnoea in the majority of cases is reached when the breathing reserve is between 60 and 70 per cent of the maximum breathing capacity.

(*2*) It is obvious that the lower the ratio $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ at rest, the lower it will be during and after completion of the standard exercise. An attempt was made to establish a correlation between the ratio $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ at rest and the presence and severity of dyspnoea during the recovery period following exercise, in 129 patients, including the previous group, and in addition in some patients with chronic pulmonary disease, but without any clinical evidence of cardiocirculatory failure (chart 2). In 54 cases where no dyspnoea was felt during the recovery period, the average breathing reserve at rest was 91.7 per cent of the maximum breathing capacity with an S.D. ± 2.4; in 55 subjects who were mildly dyspnoeic (less than two minutes of the recovery period), the average breathing reserve at rest was 88.0 per cent of the maximum breathing capacity, with an S.D. ± 3.3; and in 20 cases where dyspnoea was of longer duration (two to five minutes, and in most instances from four to five minutes), the average breathing reserve was 77.9 per cent of the maximum breathing capacity with an S.D. ± 4.5. Although there is some overlapping, especially between the nondyspnoeic and mildly dyspnoeic groups, comparison between groups I and II, and II and III, shows statistical differences between their respective means that are highly significant (P less than .01) (see footnote[3]).

The study of the scattering of observations shows distinctly that, when the ratio $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ at rest is above 93, no subject is dyspnoeic during the standard exercise test; between 92 and 87, one-half of the subjects are not dyspnoeic, the other one-half being dyspnoeic for less than two minutes; between 87 and 85, all were dyspnoeic up to two minutes; between 85 and 81, the subjects were either mildly or severely dyspnoeic; and finally below 80, the dyspnoea after the standard exercise lasted at least two minutes.

Estimation of the ratio $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ at rest in

gauging the extent of ventilatory insufficiency should yield valuable information. For example, if the limits within which this ratio decreases following thoracoplasty can be established, it should be possible to predict with some degree of accuracy before operation the degree of ventilatory insufficiency to be expected after its completion.

RESPIRATORY INSUFFICIENCY

Respiratory insufficiency is concerned with disturbance in the respiratory gas interchange between alveoli and the blood in pulmonary capillaries. This is dependent upon:

(*a*) The proportion of well, poorly and nonventilated alveoli.
(*b*) The number, size and distribution of capillaries in contact with alveoli, and the speed of blood flow through them.
(*c*) The gradient of pressure of respiratory gases across the alveolo-capillary partition, and the physical properties of this partition.

Respiratory insufficiency may be present at rest or induced by exercise. It is often insidious and unrecognized. Cyanosis is its best known clinical manifestation. Yet the degree of anoxaemia and hypercapnoea (if present) and the defects in alveolar ventilation can only be determined by appropriate physiological measurements.

Determination of the *efficiency of alveolar ventilation* with regard to oxygen consumption and carbon dioxide elimination, and the study of *respiratory gases in the arterial blood*, will detect interference with respiratory gas exchange in the lungs; this may be present at rest or revealed only as the result of exercise.

A. *Efficiency of Alveolar Ventilation*

The efficiency of ventilation with regard to respiratory gas exchange may be measured by the volume of oxygen removed from, or carbon dioxide eliminated in, each liter of air ventilated. (The terms of "rate of oxygen removal" and "rate of carbon dioxoide elimination" will be used for the sake of simplification.)

Samples of gas collected in the Tissot gasometer and the Douglas bag, under basal conditions and during exercise, are analyzed in duplicate in the Haldane apparatus. The oxygen removed and the carbon dioxide eliminated are expressed as the number of cubic centimetres of gas exchanged, per liter of air ventilated. Oxygen intake and carbon dioxide output are also calculated per minute per square metre of body surface (table 1).

In table 2, data found in the literature have been tabulated (11, 12, 7). To fit the simpler expression that we adopted from Herbst (1928), the "ventilatory equivalent," used by most authors since Anthony, has been recalculated as follows: If ventilatory equivalent $= \frac{100}{O_2 \text{ consumed}}$, then rate of oxygen removal $= \frac{100}{\text{Ventilatory equivalent}}$. It will be seen that when the rate of oxygen removal is determined by gas analysis, the co-

TABLE 2

Oxygen consumption and carbon dioxide elimination per liter of ventilation at rest
*A review of values found by various authors in normal or control subjects**

AUTHORS	NUMBER OF SUBJECTS	METHOD OF DETERMINATION	MEASUREMENT			
			O_2, cc./lit. vent.		CO_2, cc./lit. vent.	
			Mean	Coeff. of variation	Mean	Coeff. of variation
			cc.	*per cent*	*cc.*	*per cent*
Knipping & Moncrieff	54	Spirometric tracings	41.0	25†	—	—
Hurtado & Boller	15	Spirometric tracings	37.5	27	—	—
Kaltreider & McCann	20	Gas analysis	41.7	—	—	—
McMichael	76	Gas analysis	44.0‡	16	36.0	14
Cournand & Richards	15	Gas analysis	46.8§	15	36.3§	16

* Values expressed as ventilatory equivalent for

$$\text{Oxygen (or } CO_2) = \frac{\text{Min. Vol. Ventil.} \times 100}{\text{Min. Vol. Ventil.} \times O_2\% \text{ Intake}} = \frac{100}{O_2\% \text{ Intake}}$$

† Approximate.

‡ Approximate (assuming room temperature to be 25°C., but calculated as dry gas at 0°C. and 760 mm. Hg.).

§ Calculated as dry gas at 0°C. and 760 mm. Hg.

efficient of variation around the mean is only about 15 per cent, as against a variation two-thirds greater when determined from spirometric tracings. Furthermore, Kaltreider and McCann (7) have shown a definite relationship between this measurement and the degree of disability observed in pulmonary fibrosis, emphysema and cardiac insufficiency. As an index of adequate relationship between alveolar ventilation and pulmonary circulation, McMichael (13) considers the rate of oxygen removal to be of significant value.

During exercise, many factors may influence the changes observed in this measurement; chiefly, of course, the severity of the exercise. It is generally assumed (14) that the relation between pulmonary ventilation and carbon dioxide eliminated is nearly linear, so that the rate of carbon dioxide elimination per liter of ventilation varies very little (*a*) from rest to exercise, and (*b*) in relation to the intensity of exercise. In contrast (14), the oxygen consumption is much more dependent upon the rate of circulation and is limited by it. In our standard exercise of short duration (one minute), the rate of pulmonary circulation probably increases at first much more rapidly than the pulmonary ventilation, which explains in part the notable increase in the rate of oxygen removal observed (from an average of 46.8 to an average of 54.8). If, however, large areas of the lungs during exercise are ventilated but not circulated, this index should remain as it is at rest, or actually decrease. On the other hand, if as a result of cardiac insufficiency the cardiac output does not increase proportionally to the ventilation during exercise, the same result should obtain. Although somewhat ambiguous on that account, and requiring a careful analysis of other factors involved, the variation of the rate of oxygen removal at rest and during standard exercise may lead to valuable information concerning the relation between pulmonary ventilation and pulmonary circulation. It should be further noted that nervous and reflex factors may also increase ventilation (and decrease rate of oxygen removal), independent of the pulmonary and circulatory state.

B. *Respiratory Gases in Arterial Blood*

Adequate correlation between alveolar ventilation and pulmonary capillary perfusion is reflected in a high percentage of haemoglobin in the oxyhaemoglobin state in the arterial blood, whether at rest or following exercise. In table 3, results in 15 control subjects with no pulmonary or circulatory disease are computed during rest and following standard exercise. The average values and variations at rest are in harmony with those observed by Dill, Edwards and Consolazio (14) in male subjects aged twenty-three to forty-five at rest. Following exercise, these values remained unchanged, confirming the conclusions of Himwich and Barr (1923) that even during severe exercise the oxyhaemoglobin saturation per cent does not fall below 95.

A decrease in arterial oxygen saturation, below normal limits, may be due to one of several causes. The most important, in chronic pulmonary

disease, is the arterial anoxaemia brought about when pulmonary blood flows through the capillaries of alveoli that are unventilated, or inadequately ventilated. Of less importance in pulmonary disease, though probably more so in cardiac failure, is the arterial anoxaemia produced by impaired diffusion of oxygen from alveoli to intracellular haemoglobin; due to congestion, oedema or other causes. A third factor, also more significant in heart disease, is retarded circulation causing pulmonary blood to be greatly unsaturated when it reaches the alveoli; and a fourth, true "shunting" of pulmonary blood from pulmonary arteries to veins by passage through vessels that have no access to pulmonary air spaces.

TABLE 3

*Arterial blood studies in a control group at rest and during early period of recovery following standard exercise**

	REST		RECOVERY	
	Mean	Standard deviation	Mean	Standard deviation
O_2 Haemoglobin Capacity, vol. %	17.1	±1.9	17.9	±1.7
$\frac{O_2 \text{ Haemoglobin Content}}{O_2 \text{ Haemoglobin Capacity}} \times 100$	96.2	±1.2	95.8	±1.3
CO_2 Content, vol. %	52.0	±2.4	47.8	±2.3
pCO_2, mm. Hg	43.7	±3.5	43.0	±2.4
CO_2 Content at 40 mm. Hg., vol. %	50.6	±2.3	46.6	±1.9
pHs†	7.43	±.02	7.40	±.03

* See table 1.
† At 38°.

There is also a tendency in normal individuals for maintenance of a constant level of carbon dioxide tension in the arterial blood, and a constant hydrogen ion concentration. This is shown in table 3. With exercise of the limited degree described, normal subjects usually show an appreciable drop in arterial carbon dioxide content, little change in carbon dioxide pressure and a small decrease in pH. There may be, however, considerable variations in these responses, even in normal subjects, due to differences in muscular development, in breathing facility, and above all in the state of physical training. The latter may affect to a marked degree the ease and efficiency of circulatory and respiratory adaptation to exercise; blood carbon dioxide levels and arterial pH are often sensitive indices of such adaptation. For example, a poorly

trained individual often shows a large increase in carbon dioxide tension after exercise, with corresponding sharp drop in arterial pH: an evidence of ineffectual cardiopulmonary adjustment.

Samples of arterial blood for respiratory gas analysis are secured at rest, and at the end of the first minute of recovery, by puncture of the brachial artery. A careful local anaesthesia, and a sharp, flat-bevel, 19-gauge needle are used in order to obtain a painless, easy puncture. The samples of blood drawn under oil are transferred into chilled bottles containing 0.6 mg. of sodium fluoride and 4.5 mg. of neutral potassium oxalate dried in autoclave. The blood is gently stirred and the pipettes for determination of oxygen and carbon dioxide content are immediately filled and analyzed in duplicate in the Van Slyke manometer. Methods for determination of oxygen capacity and carbon dioxide dissociation curves, from which pCO_2 and pH may be estimated, have been described in detail elsewhere (16).

CARDIOCIRCULATORY INSUFFICIENCY

Cardiocirculatory insufficiency, in various combinations with ventilatory and respiratory insufficiency, in the course of chronic pulmonary disease and collapse therapy, may be due to:

(*a*) Hypertension in the lesser circulation from any cause and subsequent right ventricular hypertrophy and failure.
(*b*) Obstruction to the flow of blood by displacement and torsion of the heart and intrathoracic vessels; increased pressure in the thoracic cavity; or disturbed mechanics of breathing. These changes may influence the cardiac output, the speed of circulation and favor pulmonary congestion.
(*c*) The effects of anoxaemia upon the cardiac muscle and upon the cardiovasomotor centres.
(*d*) Independent cardiac disease.

The measurement of the arterial blood pressure, the venous pressure, pulse rate, circulation time and the vital capacity, both at rest and following increase of the blood volume by a rapid saline infusion (17, 18), and the electrocardiogram are the chief data which we have used to estimate cardiocirculatory performance. In some instances these measurements may be repeated following exercise.

The technique is carried out as follows:

The patient being in a nearly recumbent position, the venous pressure apparatus of the water-manometer type is connected to the side opening of a

three-way stopcock. The zero point for venous pressure is taken arbitrarily as a level 5 cm. below the angle of Louis. The circulation time is measured from arm to carotid sinus (NaCn) (21), or from arm to tongue (calcium gluconate) (22). Vital capacity is obtained by having the subject connected to a Benedict-Roth metabolism apparatus, and recording several tracings of maximal breaths.

The artificial increase of blood volume (19) is produced by infusion of 1,500 cc. of an isotonic saline solution in 30 minutes, the infusion tubing being connected to the three-way stopcock. Venous pressure, circulation time and vital capacity are measured before the infusion is started and at the end of the infusion. The variations in venous pressure are followed closely, by measuring its level every two minutes.

The normal range of venous pressure lies between 30 and 100 mm. of water. Altschule (20), in a group of 83 normal subjects, found the venous pressure to lie below 100 mm. in all cases but 3. This coincides with our experience, and 100 mm. water can be assumed to represent the upper limit of normal venous pressure. Sufficient time (at least five minutes) must be allowed to elapse between the insertion of the needle (gauge 17) and the reading. Following the 1,500 cc. infusion in normal subjects, the level of venous pressure increases but little, at most 30 to 35 mm. water, and remains below 100 mm. water. If the rise is greater, it is thought to represent failure of the right heart to accommodate an increase in blood volume.

The high limit of normal of the circulation time is considered to be eighteen seconds (21). Following the infusion test, it hardly changes more than one or two seconds in normal subjects; a prolongation over five seconds is considered abnormal.

Decrease of the vital capacity following the infusion test is evidence of pulmonary congestion. This may be related to the failure of the left heart to accommodate an increase in blood volume, or to other causes affecting the flow of blood in the pulmonary veins, or to the vasomotor state of the pulmonary capillaries. In normal subjects the per cent decrease from pre-infusion values is insignificant. More than an 8 per cent decrease can be considered as an evidence of pulmonary congestion.

SUMMARY

A simple classification of pulmonary insufficiency is offered. This consists of the division into ventilatory insufficiency, respiratory insufficiency and forms associated with cardiocirculatory insufficiency.

Physiological principles involved in this differentiation and methods of measurement are reviewed and discussed.

Ventilatory insufficiency is measured by decrease in maximum breathing capacity, or more exactly decrease in breathing reserve. The relation existing between breathing reserve and dyspnoea in pulmonary disease is stressed.

Respiratory insufficiency is indicated by (*a*) decrease in arterial oxygen saturation, (*b*) decrease in percentage removal of oxygen from inspired air or percentage elimination of carbon dioxide in expired air.

In addition to the recognized tests of cardiac function, latent cardiocirculatory insufficiency may be revealed by simultaneous measurements of the blood pressure, venous pressure, circulation time and vital capacity before and following a rapid saline infusion.

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THROMBOSIS OF THE PULMONARY ARTERY[1,2]

J. WOODROW SAVACOOL AND ROBERT CHARR

In the present communication are reported certain observations concerning the right-sided preponderance of antemortem thrombosis of the pulmonary artery in tuberculous patients.

Material: The material studied consists of 12 tuberculous patients who showed massive thrombosis of the pulmonary artery at autopsy. In addition, 88 cases reported in the literature by 52 authors (2 to 56) are briefly reviewed. The résumé of the clinical and pathological findings of these hundred cases are listed in tables 1 and 2.

Only cases with a large thrombus, almost or completely occluding the main trunk of the pulmonary artery or its main branches, were included in this study. The thrombus was designated as right or left-sided only when it was definitely unilateral. When the thrombus had extended into the trunk from one artery it was classified as one-sided, whereas if it extended into both arteries as well as the trunk, it was considered bilateral.

Findings: In our series of 12 cases, 8 showed thrombi in the right pulmonary, only 2 in the left pulmonary artery, and 2 in both arteries. There seems to be no doubt as to their being antemortem thrombi. Their gross shape and size in relation to the lumen and shape of the involved arteries, the tenacity of their adherence to the intima of the vessels, invasion of the thrombi by strands of connective tissue from the intima and the general histological structure of the deposition of the platelets, fibrin and other cellular elements of the blood excluded any possibility of these being emboli or postmortem thrombi.

The primary site of thrombosis in these cases appeared to be the terminal ends of the first branches of the main pulmonary artery. Often the first branch of the pulmonary artery was imbedded in the area of tuberculous consolidation or firmly encased within the fibrotic walls of

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tuberculous cavities. Histological examination of these thrombi showed that the terminal portions of the thrombi appeared older, suggesting that

TABLE 1

CASE NUMBER	AGE	SEX	AUTOPSY NUMBER	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
1	58	M	251	Main trunk and both arteries	Anthracosilicosis; pulmonary tuberculosis	Thrombosis and endarteritis obliterans of vessels near right upper lobe cavity
2	62	F	357	Left artery	Pulmonary tuberculosis	Diffuse fibrosis of left lung; disease older than on right side
3	32	F	361	Right artery	Pulmonary tuberculosis	Giant cavity in right lung
4	47	M	363	Right artery	Anthracosilicosis; pulmonary tuberculosis	
5	58	M	371	Right upper lobe branch	Anthracosilicosis; pulmonary tuberculosis	Cardiac hypertrophy. Thrombus extended from tuberculous cavity
6	60	M	375	Right artery	Anthracosilicosis	Cardiac hypertrophy. Infarcts in right lower lobe
7	45	M	367	Right upper lobe branch	Anthracosilicosis; pulmonary tuberculosis	Extensive cavity in right upper lobe
8	56	M	400	Right upper lobe branch	Anthracosilicosis; emphysema and fibrosis	Progressive right ventricular failure
9	31	M	402	Right artery	Anthracosilicosis; pulmonary tuberculosis	Thrombi older in smaller pulmonary vessels. Myocardial degeneration
10	52	M	421	Right artery	Anthracosis; pulmonary fibrosis and tuberculosis	Myocardial degeneration and aortic dilatation
11	37	F	430	Left artery	Pulmonary tuberculosis	Left pneumothorax five years with uncollapsed cavity. Marked left-sided fibrosis
12	44	F	450	Left upper lobe and right upper lobe branches	Pulmonary tuberculosis	Cardiac hypertrophy and dilatation. Right ventricular mural thrombus

the thrombi began in the terminal ends and gradually grew toward the main trunks. In all our cases the thrombi were on the side in which the pulmonary disease was more marked. In 2 of our cases in which the

TABLE 2

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Helie (2) (1837)	65 F	Main trunk and both arteries	Cardiac failure	Cardiac hypertrophy and chronic passive congestion
Kidd (3) (1856)	26 F	Left lower lobe branch. Small thrombi in both arteries	Lung abscess in right lower lobe	Postpartum two weeks at onset of symptoms. Died two weeks later
Blachez (4) (1866)	29 F	Right artery	Rheumatic fever and pericarditis	Right ventricle dilated and hypertrophied
Elbogen (5) (1884)	44 M	Main trunk	Pulmonary atheromatosis	Right side of heart dilated and hypertrophied. Pulmonary artery dilated
Ferraro (6) (1886)	23	Right artery	Mitral stenosis	Cardiac failure
Dickinson (7) (1897)	4½ M	Main trunk and both arteries	Congenital heart disease	Congenital pulmonary stenosis and patent interventricular septum
v. Jurgenson (8) (1899)	60 M	Both arteries	Emphysema	
McPhedran and Mackenzie (9) (1903)	55 M	Branches to right lower and middle lobes	Emphysema, arteriosclerosis, chronic pneumonia in right lower lobe	Jaundice, syphilis of liver, infarction in right lower lobe. Possible syphilis of pulmonary artery
Hart (10) (1905)	F	Main trunk and both arteries. Older on right	Mitral stenosis	Marked cardiac hypertrophy. Thrombi in right auricle
Hart (10) (1905)	M	Main trunk and right artery	Pyelonephritis, tabes dorsalis	Thrombus in left crural vein. No pulmonary pathology noted
Monckeberg (11) (1907)	56 M	Main trunk and right artery, small left branch	Pulmonary arteriosclerosis	Right ventricular hypertrophy. Thrombus in vena cava. Cardiac decompensation
Ittameier (12) (1907)		Right branch	Aortic stenosis and insufficiency	Emphysema

TABLE 2—*Continued*

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Nedderson (13) (1908)		Right and left branches	Mitral stenosis and insufficiency; pulmonary arteriosclerosis	
Kraus (14) (1909)	30 M	Main trunk and right artery		Right ventricular hypertrophy and dilatation
Stadelmann (15) (1909)	27 M	Both arteries and branches	Pulmonary arteriosclerosis; mitral stenosis and insufficiency	Cardiac decompensation. Believes thrombosis started from sclerosis
Funke (16) (1910)	M	Right artery	Pulmonary tuberculosis	Cyanosis and swelling of face, neck and arm, worse on right
Funke (16) (1910)	35 M	Right artery	Gangrene of foot; general paresis	Thrombus terminal complication
Smith (17) (1913)	50 M	Main trunk, both main arteries, right ventricle	Anthracosis, pulmonary tuberculosis, chronic nephritis	Thrombi separate, one side from the other
Hoffmann (18) (1916)	39 M	Main trunk and right artery	Pulmonary atheromatosis	Right heart hypertrophied. Pulmonary artery dilated
Lutembacher (19) (1917)	32 F	Right artery	Mitral stenosis; patent foramen ovale	Right heart dilated. Thrombus in inf. vena cava and right auricle
Letulle and Jacquelin (20) (1920)	58 M	Right artery and branches	Pulmonary tuberculosis; right apical cavity; aneurysm of pulmonary artery	Syphilis also present
Billings (21) (1921)	60 M	Both arteries	Myocardial degeneration; left pulmonary infarct	Bilateral hydrothorax
Billings (21) (1921)	60 M	Both arteries and branches	Chronic nephritis and arteriosclerosis	Right hemiplegia. Cardiac decompensation
Billings (21) (1921)	F	Right smaller branches	Acute nephritis; myocardial degeneration	Postpartum one month at onset of symptoms

TABLE 2—*Continued*

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Billings (21) (1921)	60 M	Left lower lobe branch	Acute pleurisy, myocardial degeneration, arteriosclerosis	Thrombosed external jugular vein
Forster (22) (1922)	50 F	Right artery	Tricuspid insufficiency	Right heart hypertrophy and pulmonary infarct
Lowenstein (23) (1922)	51 M	Both arteries and branches	Patent foramen ovale	Cardiac symptoms one year
Herrmann (24) (1923)	33 F	Both arteries and branches	Cardiac failure; pulmonary infarct	Aorta also thrombosed. Cardiac enlargement
Allbutt (25) (1924)	M	Main trunk	Pneumonia during resolution	Sudden death following development of symptoms over one week
Eiman (26) (1924)	81 M	Main trunk and right artery	Healed tuberculosis; chronic purulent bronchitis—right	Thrombi in right renal artery and aorta. Dilated right heart
Rouslacroix and Perrimond (27) (1925)	56 M	Right artery	Bronchitis and emphysema	Right ventricular dilatation and hypertrophy. Pulmonary artery dilated
Schramm (28) (1927)	49 F	Right artery extending into lower lobe branch	Pulmonary atherosclerosis; mitral stenosis	Dilated pulmonary artery
Pick (29) (1927)	64 F	Main trunk and both arteries	Mitral stenosis and insufficiency	Pulmonary infarct. Thrombi in aorta and iliac arteries
Ljungdahl (30) (1928)	51 F	Right artery and branches	Pulmonary sclerosis	Right heart enlarged
Ljungdahl (30) (1928)	38 F	Right artery	Cardiac decompensation; syphilis	Right heart dilated and hypertrophied
Samek (31) (1928)	63 F	Right and left branches	Right pleural effusion; dilated right heart	Thrombus—left renal and right femoral veins
Meldolesi and Dionisi (32) (1929)	25	Right artery	Mitral stenosis	Cardiac failure
Barnes and Yater (33) (1929)	34 M	Both arteries, larger on right	Bronchiectasis; lung abscess—right upper lobe	Thrombus believed two years old. Syphilis also present

TABLE 2—*Continued*

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Jump and Baumann (34) (1929)	48 M	Main trunk and both arteries	Pulmonary tuberculosis and atherosclerosis of pulmonary artery	Cardiac failure. Dilatation of right ventricle and pulmonary artery
Goedel (35) (1930)	59 M	Main trunk and right artery		Right ventricle enlarged
Goedel (35) (1930)	50 M	Medium-sized branches right and left	Cardiac failure	
Arrigoni (36) (1930)	63 F	Both arteries	Mitral endocarditis and stenosis; pulmonary arteriosclerosis	Thrombi in right femoral artery and vein
Desclin (37) (1930)	41 M	Both arteries and branches		Old thrombus in right femoral vein. Small thrombi in right ventricle
Desclin (37) (1930)	62 F	Main trunk and both arteries	Carcinoma of mediastinal lymph nodes	
Desclin (37) (1930)	45 F	Right artery and small left lower lobe branch		Thrombosis of right femoral vein. Cardiac enlargement
Desclin (37) (1930)	49 F	Right artery and left upper lobe branch	Thrombophlebitis of both lower extremities	Right ventricular hypertrophy
Desclin (37) (1930)	65 F	Right artery	Mitral stenosis and insufficiency	Thrombosis left femoral vein
Desclin (37) (1930)	58 F	Right artery and branches	Carcinoma of oesophagus	Both femoral veins thrombosed
Desclin (37) (1930)	56 F	Both upper lobe branches	Carcinoma of breast	Postoperative death
Desclin (37) (1930)	45 M	Both branches		Both femoral veins thrombosed
Desclin and Regnier (38) (1931)	53 M	Right artery	Right lower lobe lung abscess and peripheral gangrene; syphilitic aortitis	Cardiac degeneration and hypertrophy. Dilatation of right heart especially. Femoral thrombosis bilaterally

TABLE 2—*Continued*

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Desclin and Regnier (38) (1931)	55 M	Main trunk and both arteries	Bronchopneumonia; small lung abscess	Femoral thrombosis. No cardiac involvement
Means and Mallory (39) (1931)	60 M	Right artery	Arteriosclerotic heart disease	Cardiac dilatation and hypertrophy. Bronchial arteries hypertrophied
Brenner (40) (1931)	58 F	Right lower lobe branch and small branches	Chronic bronchitis and emphysema	Right ventricular dilatation and hypertrophy. Infarct in right lower lobe
Brenner (40) (1931)	49 F	Both lower lobe branches	Old rheumatic fever; chronic bronchitis and emphysema	Cardiac hypertrophy and dilatation
Brenner (40) (1931)	58 M	Bilateral small branches	Chronic bronchitis and emphysema	Dilatation of pulmonary artery. Cardiac hypertrophy. Coronary and pulmonary sclerosis
Brenner (40) (1931)	56 M	Right lower lobe branch	Gastric carcinoma; chronic bronchitis and emphysema	Died without operation. Dilatation and atheromatosis of pulmonary artery
Brenner (40) (1931)	46 F	Right lower lobe branch	Mitral stenosis	Atheroma in pulmonary artery. Cardiac hypertrophy, more marked on right side
Brenner (40) (1931)	60 M	Branches to right upper and lower and left lower lobe	Chronic bronchitis and emphysema; arteriosclerosis	Pulmonary artery dilated and atheromatous
Boswell and Palmer (41) (1931)	39 M	Right artery with extension to left	Acute respiratory infection	Peripheral and left parts of thrombus newer. Thrombosis probably began with infection
Lutembacher (42) (1933)	20 M	Right artery	Mitral stenosis and pulmonary arteritis	Pulmonary infarcts. Dilated right ventricle

TABLE 2—*Continued*

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Fowler (43) (1934)	52 M	Both arteries	Chronic bronchitis	EKG—inverted T-wave in II and III. Right axis deviation
Kampmeier (44) (1934)	46 F	Right artery and right lower lobe branches	Mitral stenosis; patent foramen ovale	Right heart dilated. Thrombus in inferior vena cava and right auricle
Montgomery (45) (1935)	36 F	Both arteries	Pleurisy; Ayerza's syndrome	History of symptoms since delivery eight years previously
Sprague and Mallory (46) (1936)	50 F	Both arteries and branches	Pulmonary endarteritis and cor pulmonale	Heart failure
Ameuille *et al.* (47) (1936)	35 M	Right lower lobe branch	Pulmonary tuberculosis both upper lobes	Intestinal tuberculosis. Partly organized atelectatic area in right lower lobe
Ameuille *et al.* (47) (1936)	35 F	Main trunk and both arteries	Pulmonary tuberculosis	Giant cavity in left upper lobe
Ameuille *et al.* (47) (1936)	36 M	Left lower lobe branch	Pulmonary tuberculosis	Intestinal tuberculosis
Lutembacher (48) (1937)	36 M	Right artery	Mitral stenosis; pulmonary arteritis	Pulmonary artery dilated. Pulmonary infarcts
Lutembacher (48) (1937)	35 F	Both arteries and lower lobe branches	Mitral stenosis	Pulmonary artery dilated. Atelectasis of part of left lower lobe
Lutembacher (48) (1937)	32 F	Right artery	Mitral stenosis	Right ventricle dilated and hypertrophied
Mohler and Crawford (49) (1937)	40 F	Left lower lobe branch	Mitral stenosis	Cardiac hypertrophy and multiple pulmonary infarcts
Mohler and Crawford (49) (1937)	50 F	Left artery	Congestive heart failure; myocardial fibrosis	Multiple small infarcts
Mohler and Crawford (49) (1937)	52 F	Right lower lobe branch	Cardiac hypertrophy	Congestive heart failure
Mohler and Crawford (49) (1937)	64 M	Right artery	Anthracosis, pulmonary fibrosis	Cardiac hypertrophy and dilatation

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TABLE 2—*Concluded*

AUTHOR AND YEAR	AGE AND SEX	LOCATION OF THROMBI	PRINCIPAL DIAGNOSIS	REMARKS
Mohler and Crawford (49) (1937)	52 F	Right artery	Hypertension, obesity, fibromyoma uteri	Cardiac hypertrophy. Thrombi of right femoral and iliac veins
Mohler and Crawford (49) (1937)	16 F	Bilateral smaller branches	Pulmonary abscess —left lower lobe	Empyema
Mohler and Crawford (49) (1937)	50 M	Right artery	Pulmonary carcinoma	Right artery compressed by growth
Mohler and Crawford (49) (1937)	40 F	Right artery	Pneumonia and left empyema	Small infarct. Thrombus in right auricle
Arel and Saka (50) (1937)	54 M	Right artery, branch on left	Pulmonary tuberculosis	Tuberculous changes in vessel wall. Aneurysm of pulmonary artery in right lower lobe branch
Liebermeister (51) (1937)	47 M	Both arteries	Mitral stenosis; pulmonary tuberculosis and bilateral pneumothorax	Patent foramen ovale. Dilated pulmonary artery
Markoff (52) (1938)	34 M	Right artery	Mitral stenosis and insufficiency	Right heart hypertrophy. Terminal jaundice and pulmonary infarct
Markoff (52) (1938)	59 F	Right branches	Purulent bronchitis; myocardial degeneration	Terminal gangrene —right upper lobe
Barsoum (53) (1938)	31 F	Main trunk and both arteries	Paroxysmal tachycardia	Possibly small emboli with gradual accretion. Postpartum death
Barsoum (53) (1938)	50 F	Main trunk and both arteries	Chronic bronchitis; pulmonary atherosclerosis	Pulmonary fibrosis
Means and Mallory (54) (1938)	71 M	Right lower and upper lobe branches, left smaller branches	Pulmonary thrombosis	Popliteal phlebitis. Thrombus in inferior vena cava
Manaugh (55) (1939)	60 M	Right artery extending into middle and lower lobe branches	Chronic arthritis	Thrombus in right auricular appendage. Mistaken for coronary attack
Wade (56) (1940)	59 M	Main trunk and both arteries, separate thrombi	Pulmonary anthracosis and fibrosis; cardiac hypertrophy	EKG—inverted T-wave in leads II, III, and IV. Right heart dilated

thrombi were on the left side, one had had artificial pneumothorax on that side for five years and the other showed marked fibrosis of the left lung as the result of pleural effusion on that side.

In 2 cases in which the thrombi were on both sides, the thrombus on the right side looked older both grossly and histologically. In these cases the tuberculosis was more advanced and chronic on the right side. Evidently the thrombus formed first on the right side and later extended into the left side.

Among the 88 cases collected from the literature (table 2) the thrombi were in the right pulmonary artery in 41, in the left pulmonary artery in 4 and in both arteries in 43. Regarding the cases of bilateral thrombosis, several authors stated that the thrombi on the right side appeared older. Myocardial insufficiency appeared to be more frequently associated with bilateral thrombosis.

DISCUSSION

In the entire series of 100 cases, 49 showed thrombosis on the right side, 45 on both sides and only 6 on the left side. The preponderance of thrombosis in the right pulmonary artery or the infrequency of this condition on the left side may be dependent upon certain anatomical differences about the roots of the lungs (figures 1 and 2). On the right side, according to Senior (57), the pulmonary artery is longer than the left and lies horizontally under the arch of the aorta. In its course to the hilum, the right pulmonary artery has certain structures close to it which the left artery does not possess. In front there is the ascending aorta and the superior vena cava, as well as the phrenic nerve, anterior pulmonary plexus and the reflexion of the pleura. Lying close to the artery posteriorly is the right bronchus and the azygos vein. Below the artery is the right atrium and the upper right pulmonary vein. Above the artery is the arch of the aorta. At the root of the lung, the right bronchus is above and behind it and the pulmonary veins below and in front of it.

On the other hand, the left pulmonary artery does not have such close relationship to the various structures. It is shorter and slightly smaller and passes in front of the descending aorta. At the root of the lung the left bronchus lies below and behind the artery and the pulmonary veins lie in front (figures 1 and 2). The left pulmonary artery does not have the ascending aorta and superior vena cava in front as has the right pulmonary artery. Neither has it the arch of the aorta above it and the

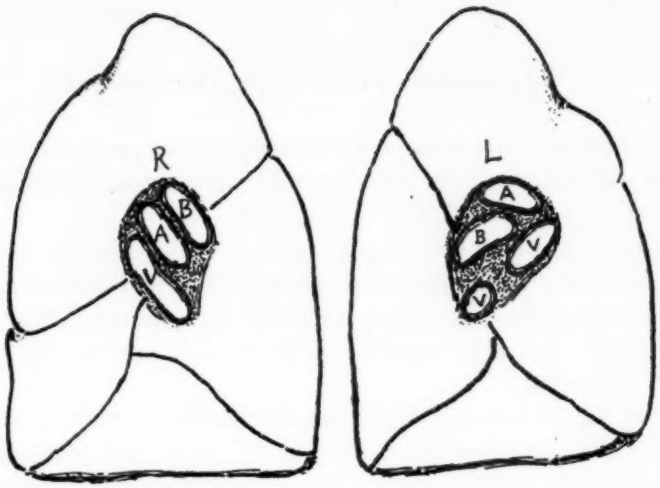

FIG. 1

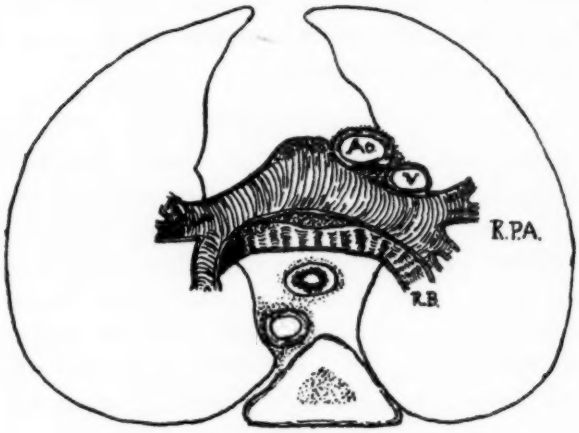

FIG. 2

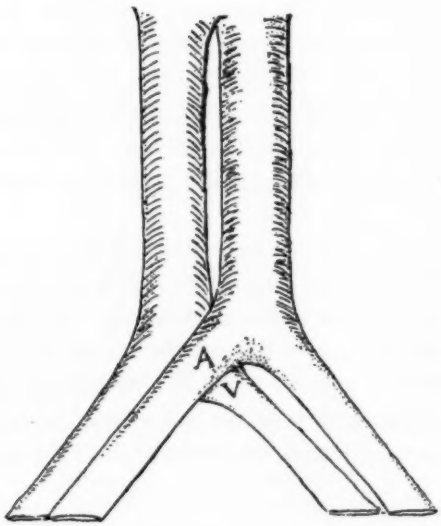

FIG. 3

FIGS. 1–3

left atrium and the right pulmonary veins below it as has the right pulmonary artery. So, too, the azygos vein which lies behind the right pulmonary artery is not present on the left side.

For these reasons the left pulmonary artery may be less influenced by pathological conditions of the lungs and aorta. In chronic pulmonary tuberculosis there is frequently marked traction upon and distortion of the trachea and bronchi and in cardiovascular disease the aorta is occasionally enlarged or sometimes displaced. Such processes would have much more effect on the right pulmonary artery than on the left, since the aorta arches over the right and is unrelated to the left artery; the right bronchus is more nearly adjacent to the right artery than the left bronchus is to the left artery. Other structures such as the right atrium and superior vena cava may also be of importance in this connection. External pressure from contiguous structures may produce narrowing of the arterial lumen, thus reducing the velocity of blood flow and aiding thrombosis.

Substantiating the above view that an artery lying over a vein may slow up the velocity of blood flow, thereby aiding thrombosis, are several cases of unilateral oedema of the ankles in pulmonary tuberculosis observed by us. In these cases the swelling was present only in the left ankle and leg. There were patients with bilateral swelling of the legs and, even among these, the oedema was more marked on the left side. Of five autopsied cases, one showed a large antemortem thrombus in the left common iliac vein above and below the point over which the right common iliac artery crossed.

It seems that the pressure exerted upon the left common iliac vein by the right common iliac artery at the point of crossing (figure 3) narrows the lumen of the vein, thereby slowing the venous blood flow and favoring thrombus formation. Slowing of blood flow with definite pooling or stagnation of the blood-stream, resulting either from pressure upon the vessel or from constriction of the blood vessel by intrinsic vascular disease, has been considered by Aschoff (58) as a definite aetiological factor in thrombosis.

FIG. 1. Schematic drawing of the right (R) and left (L) hilum regions showing the relations of the pulmonary arteries (A) to the bronchi (B) and the pulmonary veins (V). On the right side pulmonary artery is "squeezed" between the bronchus and pulmonary vein.

FIG. 2. Schematic drawing of the cross section through the roots of lungs showing the aorta (Ao) and superior vena cava (V) anterior to the right pulmonary artery (R.P.A.) and the right bronchus (R.B.) behind it.

FIG. 3. Schematic drawing of the right common iliac artery (A) crossing over the left common iliac vein (V), interfering with the venous blood flow through the left iliac vein.

Several authors mentioned that among the cases of bilateral thrombosis, the thrombi on the right side looked older. This certainly was so in our 2 cases. From this we have inferred that, probably in a considerable number of cases of bilateral thrombosis, the thrombus on the left side was the continuation or extension of the thrombus in the right pulmonary artery. The frequent association of myocardial insufficiency with bilateral thrombosis suggests that lack of propelling force of the blood-stream tends to encourage relatively rapid development of the thrombus into the trunk and left pulmonary artery.

In our earlier study (1) we have reviewed various hypotheses advanced in regard to the pathogenesis of thrombosis of the pulmonary artery. Degeneration and inflammation of the artery, endarteritis, chemical changes of the blood due to the destruction of the pulmonary tissues, hyperinosis, increased coagulability of the blood, increased blood calcium, polycythaemia, dehydration and anoxaemia, bacterial infection of the vessel, tumor cell invasion of the vessel and myocardial insufficiency are considered aetiological factors. It was suggested that, in our opinion, pulmonary diseases such as tuberculosis and silicosis were important aetiological factors. In our series, tracing the thrombosed artery toward the periphery invariably showed that its terminal branches containing thrombi ended as blind pouches. These terminal parts were located either at the centre of the tuberculous or silicotic consolidation or at the wall of the consolidated area.

However, pulmonary disease is not the only determining factor in the production of thrombosis. Of the 100 cases there was definite evidence of parenchymal pulmonary disease in 46, not including those with pulmonary arterial changes associated with cardiovascular disease. In this series of 46 cases, 22 had the thrombus on the right side, 19 bilaterally and 5 on the left side. In the remainder of the 100 cases there was no pulmonary disease. Twenty-seven of these had the thrombus on the right side, 26 bilaterally and one on the left side. This suggests that the right-sided predominance of thrombosis does not depend entirely upon pulmonary disease being more marked on that side but rather upon other factors such as those mentioned above.

The principal clinical features of the 12 cases in our series were increasing dyspnoea, cyanosis, pain in the chest or epigastrium, mental confusion, restlessness, engorgement of the cervical veins, exophthalmos with blurred vision, low pulse pressure with fine thready pulse and

oedema of the ankles in the terminal stages. Marked dyspnoea and cyanosis, as presented by these patients, are rare in uncomplicated pulmonary tuberculosis. Dyspnoea increased steadily and the patients had to be propped up in bed. The cyanosis was most marked about the face; its intensity was comparable to that of *cardiacos negros* of Ayerza's syndrome.

Pain was a prominent symptom in all cases. Not all had the pain in the chest or on the same side as the thrombosis. The pain was deep-seated and vague in its location. The most common area appeared to be the substernal region. In 2 patients the pain began in the epigastrium, later extending into the substernal region.

Restlessness and mental confusion were striking. Most of the patients tossed about in bed. At times they were slightly confused as to time and place. Mental confusion was probably dependent upon cerebral ischaemia. Kampmeier (44), Billings (21) and Schramm (28) attached considerable significance to this symptom.

In 3 cases exophthalmos developed as dyspnoea and cyanosis became severe. The conjunctival vessels became engorged. Blurred vision accompanied exophthalmos which probably resulted from oedema of the retrobulbar areolar tissues and retinal congestion. Low pulse pressure with thin thready pulse was present in most patients. Ankle oedema of varying degree was present in all. It was most marked in the cases with thrombosis of both pulmonary arteries. The liver was palpable when there was bilateral ankle oedema, suggesting pronounced myocardial insufficiency.

In 4 of our series the lungs with the thrombosed pulmonary arteries showed practically no pulmonary tissues because of the extent of the excavation. Yet the occlusion of the vessels supplying these shell-like structures produced most acute dyspnoea, cyanosis and pain in the chest. The possibility of neurogenic factors in the production of such symptoms in association with pulmonary embolism has recently been emphasized by deTakats (59). A similar mechanism may play a part in producing these symptoms in thrombosis.

The clinical significance of the thrombosis of the pulmonary artery in tuberculosis appears to be the close similarity of the symptoms of this condition to those presented by massive spontaneous pneumothorax. Careful examination of the chest both physically and roentgenologically was helpful in differential diagnosis.

SUMMARY AND CONCLUSIONS

1. Twelve cases of massive thrombosis of the pulmonary artery complicating tuberculosis were studied clinically and at autopsy.

2. In 8 the thrombus was in the right pulmonary artery, in 2 in the left artery and in 2 in both arteries.

3. Review of 88 reported cases showed a similar preponderance of thrombosis in the right pulmonary artery and definite infrequency of the condition in the left artery.

4. Even when there was a thrombus in both arteries, the one in the right artery looked older, suggesting that it originated there.

5. It was suggested that the preponderance of thrombosis in the right pulmonary artery and its infrequency in the left artery might be dependent upon the anatomical relation of the arteries to their adjacent structures. On the right side the artery is crossed over by the arch of the aorta and at the hilum it is "squeezed" between the vein and bronchus. On the left side the artery is relatively free.

6. The outstanding clinical features are dyspnoea, cyanosis, pain in the chest, restlessness, mental confusion, weak thready pulse, low blood pressure and ankle oedema. This condition simulates spontaneous pneumothorax complicating pulmonary tuberculosis.

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LEUCOCYTE COUNT AND RECOVERY FROM TUBERCULOSIS[1]

Correlation of Neutrophile Polynuclears, Lymphocytes, Monocytes and the Medlar Index with Recovery from Tuberculosis at Different Altitudes above Sea Level

C. H. BOISSEVAIN AND E. N. CHAPMAN

In the year 1936 a study was published by Boissevain, Forster and Good (1) on the correlation of blood counts with recovery from tuberculosis. This study covered 1,569 blood counts made on 431 patients at Cragmor Sanatorium, Colorado Springs, Colorado, during the years 1923–1932. The highest correlations,[2] both with condition on leaving the sanatorium and with subsequent condition (1934), were found for the number of neutrophiles (−.320 and −.408) and with the Medlar Index (−.400 and −.371). No significant correlation was found with the number of lymphocytes or monocytes. These results were criticized by Smithburn, Sabin and Hummel (2) who considered the total of counts per patient insufficient. The statistical basis for this criticism is not clear, for when each count is correlated with the condition of the patient, as was done in that study, the random variation in each count is compensated by random variations in the opposite direction. This makes the total number of counts and the standard deviation the only measures of accuracy. The total number of patients considered is similarly the measure of the elimination of individual differences between patients.

[1] From the Colorado Foundation for Research in Tuberculosis at Colorado College, Colorado Springs, Colorado.

[2] For the benefit of readers not accustomed to the use of the correlation coefficient, this number is used to measure the amount of correlation between two variables. In perfect correlation this coefficient becomes ±1.00. An example of very high positive correlation is, for instance, that between temperature and pulse-rate. If the increase in pulse-rate were always exactly proportional to the increase in temperature, their correlation coefficient would be +1.00. The fall in barometric pressure with increasing altitude is an example of a high negative correlation. A correlation of ±.5 is regarded as of considerable significance whereas a correlation below ±.25 is considered as of little value though when a large number of data are considered even low correlation coefficients acquire significance. The significance of a correlation coefficient can best be stated in terms of its standard error (given between brackets in the tables). An error equal to the standard error is likely to occur in normal distributions once in three times, one equal to two times the standard error once in twenty-five times and one equal to three times the standard error once in four hundred times.

These authors further doubted the reliability of the questionnaire method of ascertaining the condition of the patient after leaving the sanatorium and pointed out that the results from a study on a group of patients, consisting mainly of far advanced cases, was not necessarily applicable to less advanced cases. On the basis of their findings in experimental tuberculosis in rabbits, they maintained that the number of monocytes and lymphocytes and their ratio were of greatest value in prognosis, but that no importance could be attached to the number of neutrophiles. In this connection it should be pointed out that it is not quite permissible to apply the findings in miliary tuberculosis in rabbits to chronic pulmonary tuberculosis in man. On the other hand, Elwood and De Cecio (3) have found that, in human lung tuberculosis, lymphocytes and monocytes do not reflect significant developments, while a trend of a neutrophile leucocytosis is indicative of the exudative process.

The present study was undertaken, in part, to decide the questions raised by Smithburn, Sabin and Hummel. Probably the most complete series of blood counts on tuberculous patients in the country is the one that has been carried on for the past fifteen years at the Metropolitan Life Insurance Company Sanatorium at Mt. McGregor, New York, under the supervision of Dr. E. M. Medlar. Through the kindness of Doctor Ordway, Medical Director of the Sanatorium, this series was made available to us for study. The material used consists of 8,684 blood counts made on 204 patients during the years 1926 to 1933. The discharge condition on each of these patients was determined by the staff of the sanatorium and recorded at the time of discharge, according to the American Sanatorium Association classification, as: arrested, apparently arrested, quiescent, improved, unimproved and dead. The subsequent condition was ascertained in 1938 by the excellent follow-up system[3] of the Metropolitan Life Insurance Company and recorded as well, curing or dead. In Cragmor Sanatorium from 1923 to 1932 this classification was not used but, instead, both discharge condition and subsequent condition were recorded as cured, arrested, much improved, improved, stationary, worse or dead. After a careful comparison of these different standards, we were able to reclassify the Cragmor series (to make the correlation coefficients as closely comparable as possible)

[3] This system is most efficient since all patients are employees of the company and upon discharge from the sanatorium return to work for the company or, if unable to work, remain on disability insurance as long as disability continues. Thus the company has a complete check on the condition of practically every patient discharged from the sanatorium.

by giving it the same notations as those used at Mt. McGregor. For the Cragmor classifications of subsequent condition, cured, arrested and much improved, the one class "well" was substituted; while improved, stationary and worse became "curing." For comparing the discharge condition it was only necessary to group the two Cragmor classifications stationary and worse together as unimproved. This reclassification caused certain changes in the values of the correlation coefficients, without affecting the general picture or the conclusions that could be drawn from them. The values of the Cragmor correlation coefficients given in the succeeding tables are, therefore, the new ones and not those of the original publication of Boissevain, Good and Forster.

The patients at Cragmor were fairly equally divided over all age-groups; they were mostly referred to Cragmor by other physicians, usually from other states, which perhaps accounts for the large number of far advanced cases in this group. The patients at the Metropolitan Life Insurance Company Sanatorium are drawn from the employees of this company; many of them are young women with clerical jobs. The periodic health examinations of all employees prevent, to a large extent, the development of far advanced cases of tuberculosis. Social and educational standards of both groups were quite similar and treatment in both institutions followed the same general lines. Frequent blood counts had been made on all patients at Mt. McGregor with an average of 42 per patient. These counts and the computation of the Medlar Index had been done under the direction of Doctor Medlar.

The frequent blood counts and the follow-up system at the Metropolitan Life Insurance Company Sanatorium are obviously very well fitted to test the validity of the objections made to the Cragmor study. The difference in composition of both groups offers an important test of the value of the neutrophiles in prognosis. It is always possible to find a prognostic index that fits the series of patients that is being studied. The real test comes when this index is applied to a different group of patients. The work of Elwood and De Cecio has already confirmed the importance of the neutrophile count on one additional group and the present study offers additional confirmation.

A study was recently published by Medlar, Lotka and Spiegelman (4) regarding the value of different indices in tuberculosis with the conclusion that the Medlar Index is the best. This study was based on cases *selected* from the same series of blood counts that is the subject of the present study. Such a selection seems a dangerous procedure to us for it means

that some cases were eliminated. It is indeed essential in any kind of statistical study that all relevant cases be included. Even random sampling is beset with many pitfalls and is better avoided wherever possible. One of their groups (group 2) consisted of "patients who were on discharge from Mt. McGregor considered pathologically favorable (that is, who had a favorable Medlar Index) and who had remained at work, without relapse, more than five years." The authors then proceed to prove the accuracy of the Medlar Index; obviously, as far as this group is concerned, this result was already implied in the selection of favorable cases only. It is not clear from their study what happened to patients with doubtful or unfavorable index who had remained at work or to those with favorable index who did not recover. A study of groups of such patients would have been of great interest and might have changed the conclusions somewhat. It is the great superiority of the correlation technique that all cases with sufficient data are included.

In the present series all cases were included for which sufficient data were present, as was also done in the Cragmor series. The correlation coefficients were calculated by the computers of the Cowles Commission for Research in Economics, University of Chicago, in a similar manner as described in the paper of Boissevain, Good and Forster. The average of the series of blood counts for each patient was first determined for both the Cragmor and the Mt. McGregor series and the averages correlated with the condition on discharge and the subsequent condition. No correlation coefficients were computed for the number of eosinophiles or basophiles as previous work provides no reason to believe that either is significant.

Both series show a high and approximately equal correlation of subsequent condition and discharge condition with the number of neutrophile polynuclears and the Medlar Index (table 1), but no correlation with the number of lymphocytes. We may consider this as definitely proving the importance of the neutrophile count and Medlar Index in any group of tuberculous patients. The correlation with the number of monocytes is low for the Cragmor series but almost as high as for neutrophiles in the Mt. McGregor series. This may be due to the difference in composition of the two series or to a different technique in classifying the monocytes. A high negative correlation should be shown between monocytes and lymphocytes if the contention of Smithburn, Sabin and Hummel is correct. However, the number of monocytes shows little correlation with the number of lymphocytes in either series, somewhat higher at Cragmor

TABLE 1

Comparison of correlation coefficients—Mt. McGregor data and Cragmor data*

SIMPLE CORRELATION COEFFICIENTS	1. NEUTROPHILES		2. LYMPHOCYTES		3. MONOCYTES		4. MEDLAR INDEX		5. AGE		6. DISCHARGE CONDITION		7. SUBSEQUENT CONDITION	
	Cragmor	Mt. McGregor	Cragmor	Mt. McGregor	Cragmor	Mt. McGregor	Cragmor	Mt. McGregor	Cragmor	Mt. McGregor	Cragmor	Mt. McGregor	Cragmor	Mt. McGregor
1. Neutrophiles	1.0000	1.0000	.2709	−.0847	.5361	.7118	.8427	.8026			.4786	.6575	.4158	.5047
			(.0454)	(.0695)	(.0349)	(.0345)	(.0142)	(.0249)			(.0378)	(.0397)	(.0405)	(.0522)
2. Lymphocytes			1.0000	1.0000	.2701	.1792	−.2102	−.6110			.0246	−.0639	−.0052	−.1237
					(.0454)	(.0678)	(.0468)	(.0961)			(.0489)	(.0697)	(.0490)	(.0689)
3. Monocytes					1.0000	1.0000	.3972	.5278			.2047	.5852	.1459	.4680
							(.0412)	(.0505)			(.0469)	(.0460)	(.0479)	(.0547)
4. Medlar index							1.0000	1.0000			.4812	.5754	.4350	.5106
											(.0376)	(.0468)	(.0397)	(.0518)
5. Age									1.0000	1.0000	.0541	−.0272	.1015	−.0658
											(.0488)	(.0701)	(.0485)	(.0703)
6. Discharge condition											1.0000	1.0000	.7467	.7090
													(.0217)	(.0348)
7. Subsequent condition													1.0000	1.0000

* Figures between brackets represent standard error.

(.270) than at Mt. McGregor (.179). The correlation instead of negative is positive in both series. Without attaching too much significance to these low correlations they might be interpreted as indicating a confusion between lymphocytes and monocytes. Of far greater interest is the high correlation between the number of monocytes and number of neutrophiles found in both series (Cragmor .536, Mt. McGregor .712). This lends no support to the theory of Maximow and Weidenreich that lymphocytes and monocytes are genetically related and that the latter may develop from the former. It does suggest a close relationship between monocytes and neutrophiles, although their similar behavior in tuberculosis does not necessarily imply a genetic relationship. It is also possible that this correlation was caused by counting a certain number of promyelocytes as monocytes; the two types of cells are notoriously difficult to differentiate and the former might well be present in cases with neutrophile leucocytosis, thus causing a parallel increase in the number of monocytes and neutrophiles. It would be interesting to know if this correlation between the number of monocytes and neutrophiles occurs in other diseases as well as in tuberculosis.

MULTIPLE CORRELATION COEFFICIENTS

If we assume that all three types of blood cells, neutrophiles, lymphocytes and monocytes, have some value in predicting the outcome of tuberculosis, we can construct a regression equation to compute an index which will show the highest possible correlation with subsequent condition or with discharge condition for the present series. Such a regression equation has the general form X = A + B (polynuclear neutrophiles) + C (lymphocytes) + D (monocytes). The correlation coefficient of this index X with the condition of the patient is called the multiple correlation coefficient. They were computed for the Cragmor series as $r_{d(pml)} = .493$, meaning that the correlation of the discharge condition of the patient with an index, built up from the figures for neutrophile polynuclears, monocytes and lymphocytes, equals .493. Similarly we find for subsequent condition $r_{S(pml)} = .440$. Comparison with the values given in table 1 shows that these values, which are shown in table 2, are not significantly different from those giving the correlation between neutrophiles or the Medlar Index and the condition of the patient. We may conclude that it is impossible to build an index by linear combination of neutrophiles, lymphocytes and monocytes, that has a significantly higher correlation than that found for the neutrophiles alone.

TREND INDEX OF NEUTROPHILE POLYNUCLEARS

By calculating the correlation between the average of a long series of blood counts and the condition of the patient, as was done in this study, one important aspect of such a series is neglected. The trend of the blood counts is obviously of the greatest interest. A patient with a certain blood count and a downward trend in the number of neutrophiles

TABLE 2

*Multiple correlation coefficients**

$r_{i(jkl...)}$	CRAGMOR	MT. MC GREGOR	$r_{i(jkl...)}$	CRAGMOR	MT. MC GREGOR
$r_{d(pt)}$		.536 (.050)	$r_{d(pmt)}$		.558 (.048)
$r_{s(pt)}$		.537 (.050)	$r_{s(pmt)}$		.574 (.047)
$r_{d(pm)}$		.550 (.049)	$r_{d(ptl)}$		.536 (.050)
$r_{s(pm)}$		.528 (.051)	$r_{s(ptl)}$		.541 (.050)
$r_{d(pml)}$	.493 (.037)		$r_{d(pmtl)}$		.562 (.048)
$r_{s(pml)}$	.440 (.040)		$r_{s(pmtl)}$		.590 (.046)

p = average number neutrophile polynuclears
m = average number monocytes
l = average number lymphocytes
t = neutrophile trend index
d = discharge condition
s = subsequent condition
* Figures between brackets represent standard error.

has naturally a better prognosis than a patient with the same count and an upward trend.

The use of the slope of a smoothed curve, drawn through the successive counts, at once suggests itself as a measure of the trend. It is, however, in many cases impossible to determine such a slope, as the shape of the curve is often quite irregular; frequent reversals of trend appear typical in many cases of tuberculosis. Another possible measure of trend is

the difference between the average of the first four counts and the average of the last four counts. This eliminates the difficulty arising from an irregular trend but is still open to another objection. A decrease from 12,000 to 6,000 would give a trend index of 6, while one from 6,000 to 3,000 would give an index of 3, although the latter trend is certainly as favorable as the former. We finally used the quotient between the average of the first four counts and the average of the last four counts as index of trend; in the above cases this gives a trend index of 2 in each case. One great difficulty remains: a number of the most favorable cases come to the sanatorium with practically a normal blood count which subsequently remains normal. Despite the highly favorable implication of such a course the trend index is only 1. It is, however, possible to circumvent this difficulty by combining the trend index with the number of neutrophiles in a new index, and then determining the coefficient of multiple correlation. The trend index, thus computed, shows a low but probably significant correlation with the subsequent condition of the patient (table 3), and a still lower but possibly significant correlation with the number of neutrophiles. This led us to consider the possibility of using the trend index only in those patients who had a high neutrophile count. The correlation of trend index with subsequent result in patients with initial counts of 6,000 or more was quite a bit higher than in those with an initial count below 6,000. However, this was not the case if the dividing line came at 5,000 instead of at 6,000, making it probable that the result with the division at 6,000 is due to the accidents of random distribution.

Combination of the trend index with the neutrophile, lymphocyte and monocyte counts gave the highest multiple correlation coefficient (table 2). This correlation (.590) was not as high, however, as the .6575 correlation between the neutrophiles and the discharge condition at Mt. McGregor. It should also be noted that the correlation between discharge condition and subsequent condition was higher in both series .747 and .709 (table 1). In other words, the clinical judgment, based no doubt on the blood-picture among other things, is more accurate than an interpretation based on blood counts alone. While the number of neutrophiles is undoubtedly highly important, the interpretation of trend is perhaps better left to the clinician to be considered in conjunction with other symptoms.

TABLE 3

Correlations with trend index—Mt. McGregor data*

TYPE OF DATA	DISCHARGE CONDITION	SUBSEQUENT CONDITION
Using all available patients	.1710 (.0680)	.2859 (.0643)
Using only those patients where it was considered sufficient data existed for computing the trend	.0620 (.0874)	.2398 (.0827)
Using patients whose average neutrophile count was below 5000	.0518 (.1383)	.2773 (.1280)
Using patients whose average neutrophile count was above 5000	.1099 (.1119)	.2784 (.1044)
Using patients whose initial neutrophile count (av. of first 4 counts) was below 5000	.1015 (.1323)	.3302 (.1191)
Using patients whose initial neutrophile count (av. of first 4 counts) was above 5000	.2112 (.1111)	.3442 (.1025)
Using patients whose final neutrophile count (av. of last 4 counts) was below 5000	−.1953 (.1242)	−.0771 (.1283)
Using patients whose final neutrophile count (av. of last 4 counts) was above 5000	−.0729 (.1189)	.1828 (.1155)
Using patients whose initial neutrophile count (av. of first 4 counts) was below 5500	.0883 (.1186)	.4418 (.0962)
Using patients whose initial neutrophile count (av. of first 4 counts) was above 5500	.4490 (.1031)	.3775 (.1107)
Using patients whose initial neutrophile count (av. of first 4 counts) was below 6000	.1201 (.1109)	.3876 (.0956)
Using patients whose initial neutrophile count (av. of first 4 counts) was above 6000	.5632 (.0956)	.4596 (.1105)
Using patients whose initial neutrophile count (av. of first 4 counts) was below 6500	.1472 (.1055)	.4063 (.0900)
Using patients whose initial neutrophile count (av. of first 4 counts) was above 6500	.5212 (.1098)	.4469 (.1207)

* Figures between brackets represent standard error.

PROGNOSIS AND EFFECT OF ALTITUDE

The curves on chart 1 show the percentage of patients dying or getting well for various gradations in the total neutrophile count; they were "smoothed" to eliminate minor irregularities. The actual number of cases on which the curve is based are given in table 4, which also gives

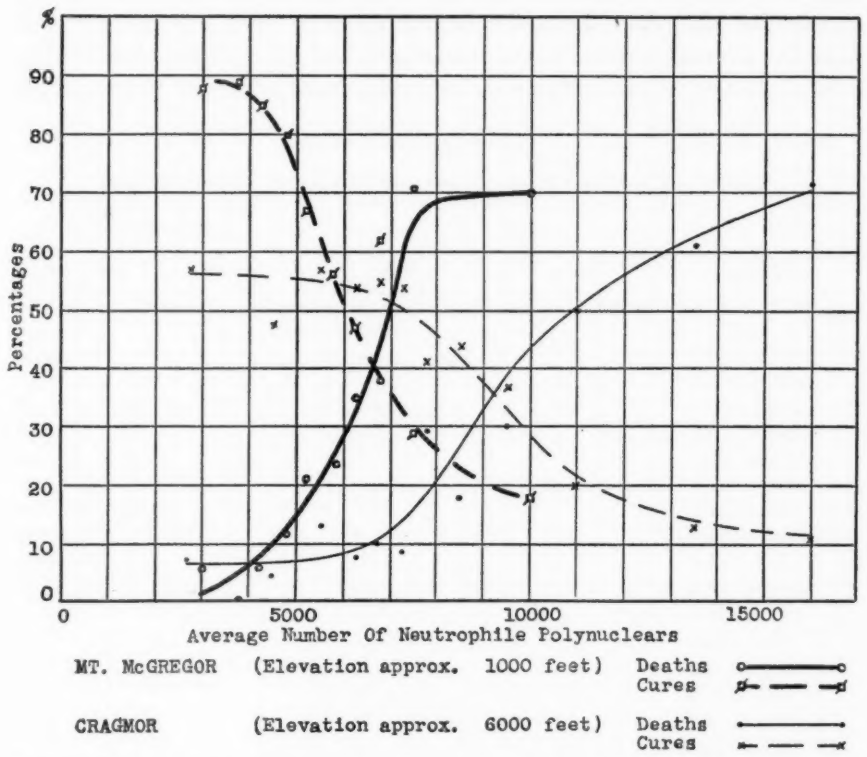

CHART 1. Comparison of percentage deaths and cures at Mt. McGregor and at Cragmor for different average neutrophile count

the number of patients still curing (group 2) which are not included in the chart.

The curves are surprisingly smooth (an indication that we are dealing with a law of nature) and show an increasing percentage of deaths with increase in neutrophiles and a simultaneous decrease in percentage of cures. Since the number of neutrophiles offers a measure of the condition of the patient, these curves make it possible to compare the end results of similar groups of patients at Mt. McGregor and at Cragmor. As

observed before, both groups of patients were treated along the same general lines by competent physicians. Cragmor, near Colorado Springs, however, is situated at 6,400 feet altitude and Mt. McGregor at only 1,100 feet. It is well known that blood counts vary with altitude. All those who have studied the subject agree that the percentage of lymphocytes increases and the percentage of neutrophiles decreases with an increase of altitude. From the figures given in table 5 it may be seen that the average percentage of neutrophiles at an altitude of 6,000 feet is 52.4 per cent, against 60.8 per cent at sea level, while the total number

TABLE 4

Number and percentage of patients and their average total neutrophile counts

NUMBER OF NEUTROPHILES	CRAGMOR						MT. MC GREGOR					
	Number			Percentage			Number			Percentage		
	Well	Curing	Dead	Well	Curing	Dead	Well	Curing	Dead	Well	Curing	Dead
1500– 2500												
2500– 3500	8	5	1	57	36	7	15	1	1	88	6	6
3500– 4000							16	2	0	89	11	0
4000– 4500							28	3	2	85	9	6
4500– 5000	10	10	1	47.5	47.5	5	21	2	3	80	8	12
5000– 5500							16	3	5	67	13	21
5500– 6000	35	18	8	57	30	13	14	5	6	56	20	24
6000– 6500	20	14	3	54	38	8	8	3	6	47	18	35
6500– 7000	11	7	2	55	35	10	8	0	5	62	0	38
7000– 7500	19	13	3	54	37	9						
7500– 8000	11	8	8	41	29.5	29.5	4	0	10	29	0	71
8000– 9000	24	21	10	44	38	18						
9000–10,000	18	16	14	37	33	30	3	2	12	18	12	70
10,000–12,000	9	14	23	20	30	50						
12,000–15,000	5	10	23	13	26	61						
15,000 and higher	2	3	13	11	17	72						

of leucocytes is somewhat decreased, giving an even greater decline in the total number of neutrophiles. This phenomenon is probably connected with the decrease in oxygen pressure, as Balo (5) found the same in animals kept under reduced pressure. In 8 rats kept for three to four days under a pressure of 200 mm. mercury, he found a decrease in the number of leucocytes with relative lymphocytosis. The percentage of neutrophiles dropped sharply, in one case to as low as 6 per cent.

We could thus expect to find less favorable results at Cragmor than at Mt. McGregor when groups with the same blood count are compared,

but this is not the case. The curves for the percentage of deaths at Mt. McGregor and at Cragmor are close together for the low blood counts but begin to separate at 4,500 and then diverge rapidly until at a neutrophile count of 7,000 to 8,000 Mt. McGregor shows 71 per cent dead and Cragmor only 18 per cent. The percentage of deaths at Cragmor then rises slowly until it reaches 72 per cent at neutrophile counts of 15,000 to 25,000.

TABLE 5

Variation of polynuclear neutrophile leucocytes with altitude

AUTHOR	LOCALITY	PERCENTAGE NEUTROPHILES	TOTAL NUMBER LEUCOCYTES	REMARKS
Staines, James and Rosenberg (6)	Cornell Medical College, sea level	63	7,000	100 male students
Miller (7)	Johns Hopkins Hospital, sea level	64.3	7,200	650 counts, students
Medlar (8)	New York City, sea level	56.6	8,200	247 counts on 18 individuals
Webb and Williams (9)	Harvard University, sea level	59.5		18 students
Average at sea level		60.8	7,467	
Staines, James and Rosenberg (6)	Colorado Springs, 6,000 feet	54.5	7,390	100 male students
Loewy (Stäubli) (10)	St. Moritz, Switzerland, 6,000 feet	52.6	6,675	Visitors to St. Moritz
Loewy (Craandijk) (10)	Davos (Switzerland), 5,000 feet	54.0	6,660	Healthy natives
Webb and Williams (9)	Colorado Springs, 6,000 feet	48.5		18 students
Average at 6,000 feet		52.4	6,908	

The curves giving the percentage of cured show a different behavior. The percentage of cured at Mt. McGregor is much larger for the lower neutrophile counts than at Cragmor, almost 90 per cent against 55 per cent, the difference being caused by the much greater percentage in the category "still curing" at Cragmor. The curve for Mt. McGregor then drops rapidly while that for Cragmor remains stationary, until at the count of 6,000 the two curves cross; from there on Cragmor shows a higher percentage of cures for all counts.

The differences between the two series could be due to a different

method in classifying the cures but this does not seem likely as the greatest differences occur in the number of deaths. Another explanation might be that the divergence between the two is due to the different composition of the two series. The Mt. McGregor series includes more young women, but a study made of the percentages of deaths for women only indicates that they are actually lower than those for the entire group. It is possible that the larger percentage of cures at Mt. McGregor in the lower neutrophile counts is due to a greater number of incipient cases there; this could account for at least some of the difference, especially when added to the 20 per cent handicap of Cragmor due to the blood changes at high altitudes. The larger percentage of cures for the higher neutrophile counts at Cragmor might be explained similarly by the presence there of a larger number of "good chronics." Also it is a fact that the unfavorable results in each series are found in the classification with fewest patients, at Cragmor in the cases with low neutrophile counts and at Mt. McGregor in the cases with high neutrophile counts. The results might have been somewhat different if more cases had been included in these categories.

However, it is difficult to see how these factors could account for the tremendous difference between 71 per cent deaths in patients running an average count of 7,000 to 8,000 neutrophiles at Mt. McGregor and only 18 per cent at Cragmor. It, therefore, seems to the present authors that none of the above explanations is sufficient to account for the differences between the two series, and that the explanation must be sought in the difference in altitude between these two sanatoria, Cragmor at 6,400 feet, Mt. McGregor at 1,100 feet. The changes in the blood-picture associated with altitude are in the same direction as those associated with recovery from tuberculosis. It is certainly not unreasonable to suppose that the same factors that influence the blood-picture will also influence the recovery from tuberculosis. It has also been shown by one of us (Chapman) in collaboration with Cowles (11) that there is a high correlation between the white death rate from pulmonary tuberculosis by states in this country and their elevation above sea level. In that study it was impossible to distinguish between the effect of altitude, relative humidity and hours of sunshine, as these three factors are closely related in this country; states with a high elevation above sea level also have low relative humidity and many hours of sunshine. In an effort to distinguish between these factors we have computed an index which measures evaporation from the lungs, assuming that any favorable effect of low relative

humidity on pulmonary tuberculosis is caused by increased evaporation from the lung. Such evaporation depends not only on relative humidity but also on temperature and altitude. The "evaporation index" measuring all these factors showed no correlation with the mortality from pulmonary tuberculosis, making it unlikely that relative humidity is an important factor.

This leaves hours of sunshine and altitude. Similar recomputation to substitute total radiation received per square centimetre for hours of sunshine and oxygen pressure for elevation above sea level, left the correlation coefficients unchanged or increased them. The reputed favorable effect of ultraviolet radiation on surgical tuberculosis is of course a strong argument for considering sunlight as the active factor. The disinfecting action of sunlight may also have epidemiological importance. Some experiments on the influence of radiation on pulmonary tuberculosis in monkeys (unpublished) throw some doubt upon the existence of any favorable effect of sunlight on this disease. Direct sunlight is considered harmful in cases of active pulmonary tuberculosis in man also.

Of the three factors which may exert a favorable effect on pulmonary tuberculosis the oxygen pressure remains to be considered. Oxygen is essential to the tubercle bacillus. It is worthy of note in this connection that all measures of collapse therapy interfere with the oxygen supply of the diseased lung and the usual dyspnoea of pneumothorax patients on exertion makes it very probable that the oxygen supply of the rest of the organism is interfered with. We have already referred to experiments showing that diminished oxygen pressure causes the same changes in the blood picture of experimental animals that are found in recovery from tuberculosis. Also Gutstein (12) found that pneumothorax in dogs caused the same decrease in neutrophiles, which dropped an average of 15 per cent in three animals. This evidence, scanty as it is (and more work is urgently needed on this subject), seems to indicate that the beneficial effect of altitude on tuberculosis is due to a change in the oxygen supply rather than to any of the other factors. Whether the important factor is low oxygen pressure or not, the figures here presented indicate that patients with a neutrophile count of 6,000 or more have a 50 per cent better chance of surviving at a high altitude than at sea level.

RESULTS

A study has been made on the correlation of blood counts with recovery from tuberculosis on two groups of patients living at different altitudes,

Mt. McGregor at approximately 1,000 feet elevation and Colorado Springs at approximately 6,000 feet elevation.

Both series show an equally high correlation between outcome of tuberculosis and either the total number of neutrophiles or the Medlar Index. Since the figure for total neutrophiles can be computed without the aid of a special calculator it is the method of choice.

The Mt. McGregor series also shows a good correlation between outcome and number of monocytes. This is not shown in the Colorado Springs series. The number of monocytes is highly correlated with the number of neutrophiles in both series.

It was shown that it is impossible to obtain by linear combination of values for neutrophiles, lymphocytes and monocytes an index having significantly higher correlation with subsequent condition of the patient than that for neutrophiles alone.

Patients with an average neutrophile count over 6,000 show a much smaller percentage of deaths at an altitude of 6,000 feet than at 1,000 feet elevation.

The authors are deeply indebted to Drs. W. H. Ordway and E. M. Medlar for putting the Mt. McGregor data at their disposal and for their helpful interest, and to the Cowles Commission for Research in Economics, the University of Chicago, for making the statistical computations (involving over 120,000 entries and computations) in their laboratory, and to Mr. Forrest Danson of this Commission for valuable advice.

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LABORATORY PROCEDURES IN INTESTINAL TUBERCULOSIS[1]

ALFRED L. KRUGER AND HARRY J. PERLBERG

Gastroenterology in pulmonary tuberculosis limits itself, from necessity, to the ileocaecal region in attempting to make an early diagnosis of intestinal tuberculosis. Pathologically, the ileum is the site of earliest involvement and this is explained on a two-fold basis: namely, the relative stasis that occurs here and the presence of an abundant lymphatic supply. Primary intestinal tuberculosis is exceedingly rare, especially in the United States, and, when found, is usually due to the bovine bacillus. Secondary intestinal tuberculosis is, on the other hand, the most frequent complication of pulmonary tuberculosis and is found in around 60 to 80 per cent of tuberculous individuals at postmortem. An analysis of 106 consecutive autopsies performed at the Hudson County Tuberculosis Hospital showed the incidence of intestinal involvement to be 61 per cent.

In the past two years, a diagnosis of intestinal tuberculosis was made by means of roentgenological studies on 110 patients with pulmonary tuberculosis. Of this number, 103 had a far advanced pulmonary lesion, 4 were moderately advanced and 3 had a primary lesion.

As emphasized by Cullen (1) and Granet (2), there is a direct relationship between positive sputum and intestinal tuberculosis. Granet, in a study of 740 patients with intestinal tuberculosis, found the sputum to be negative in 4.5 per cent of the cases. In our series, we found 6 per cent of the cases to have a negative sputum (including culture and guinea pig inoculation). Interestingly enough, there were 5 patients in this group who had had an effective collapse for nine months or more when they began to complain of loss of appetite and their weight curve showed a progressive gradual drop. We feel that any patient with a controlled pulmonary lesion who shows these symptoms should be suspected of having an intestinal complication which for some undetermined reason has become manifest. We therefore believe that, although the vast

[1] From the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Jersey City, New Jersey.

majority of patients with intestinal tuberculosis will be found to have a positive sputum, the absence of such a finding should not preclude this diagnosis.

Contrary to the findings of others, we have found that most of our patients had definite symptoms at the time that the intestinal studies were made. A careful history was taken by one of us (A. L. K.) on all the cases and in only 5 cases (4.5 per cent) was there an absence of symptoms. Forty-two of the patients (38 per cent) had a history of diarrhoea and abdominal cramps of a recurrent nature. Fifty per cent of the cases had a history of anorexia and progressive weight loss, whereas only 6 cases (5.4 per cent) showed a rising weight curve at the time of diagnosis. Nausea and vomiting was found in 26 cases, or 23 per cent. Constipation was noted in 8 per cent.

During the past eighteen months we have made a study of two laboratory procedures, the Woldman phenolphthalein test and examination of stools, to determine whether they were of any help in aiding us to establish a definite diagnosis of intestinal tuberculosis.

WOLDMAN'S PHENOLPHTHALEIN TEST

In 1938, Woldman (3) described a simple test for gastrointestinal ulceration which, in his hands, showed a high percentage of positive results. The technique consisted of giving the patient one hour before breakfast 10 cc. of a 1 per cent alcoholic solution of phenolphthalein diluted with water to 30 cc. Urine specimens were to be collected at two and four hours after the administration of the solution (a six-hour specimen was to be collected if any cardiac or renal damage was present). The urine specimens were to be examined promptly by the addition of several drops of 10 per cent sodium hydroxide solution and if free phenolphthalein is present a pink or red color will be seen.

The rationale behind the test is that normally 90 per cent of the phenolphthalein is excreted in the urine in a conjugate form which cannot be detected by immediate alkalinization of the urine. However, should there be any break in the mucosa of the gastrointestinal tract, greater absorption of the phenolphthalein occurs to the extent that free phenolphthalein is excreted in the urine and this can be detected by alkalinization of the urine.

Since Woldman's publication, a number of articles have appeared in the literature. Steigmann and Dyniewicz (4) showed that a minimum of conjugated phenolphthalein must exist in the urine before free phenol-

phthalein could be present and this minimum was 0.03 mg. per cent. They concluded that any condition which promoted an increased formation or circulation in the blood of conjugated phenolphthalein will lead to the appearance of free phenolphthalein in the urine. They performed the test on 200 cases, 56 of these having known gastrointestinal lesions, 110 being patients in the hospital with other diseases, and 34 were normal individuals. Of the known gastrointestinal cases, 78.5 per cent had a positive test. A 82.7 per cent positive result was obtained among the 110 other patients and 41 per cent of the normal cases gave a positive test. They concluded that this test could, therefore, not be considered as diagnostic for gastrointestinal ulceration. Kremer, Shore and Wiesel (5) performed the test on 137 patients and found the test to have definite limitations as it was correct in 56 per cent of the cases with gastrointestinal complaints and correct in 79 per cent of cases without gastrointestinal complaints. Suttenfield (6) studied 94 cases and concluded that the test was of no value, 23.3 per cent of their negative cases giving a positive test and 16.7 per cent of their cases with organic gastrointestinal lesions giving a positive result. Similar conclusions were arrived at by Watkin, Kirsch and Albert (7), Slutzky and Wilhelmz (8), LeVine and Kirsner (9), Banks and Barron (10), and Levin and Shushan (11).

The conclusions of the above authors were drawn from observations made chiefly on patients with ulcerations either in the stomach or duodenum. No concerted effort has thus far been made to determine whether or not the test might be of some value in diseases of the colon or terminal ileum.[2] On the assumption that the test might possibly be of some value in intestinal tuberculosis, due to the fact that nearly all such cases have an involvement of the terminal ileum where stasis does occur with consequent greater chance for contact of the phenolphthalein with the areas of ulceration, this test was used on 230 cases of pulmonary tuberculosis.

A gastrointestinal series was done on all 230 cases. The basis for the diagnosis of intestinal tuberculosis was a persistent spasm of the ileocaecal region as defined by Brown and Sampson (12). Of the 110

[2] After we had submitted this paper for publication, an article on *Woldman's Phenolphthalein Test in Intestinal Tuberculosis* by L. E. Siltzbach and H. R. Nayer appeared in the American Journal of Digestive Diseases, 1940, *7*, 519. The authors performed the test on 206 patients with pulmonary tuberculosis and arrived at the same conclusion as we did, namely, that the test was of no value in determining the presence or absence of tuberculous ulcers in the gastrointestinal tract.

patients with intestinal tuberculosis, 90, or 81.8 per cent, had a positive test, whereas 20, or 18.1 per cent, showed a negative test. Of the 120 cases in whom no intestinal lesions were found, 40, or 33.3 per cent, had a positive test, while 80, or 66.6 per cent, showed a negative test. The percentage of error in both groups was 26 per cent.

The test was performed exactly as described by Woldman. A completely impartial attitude was assumed throughout this study and the result of the test was not allowed to influence the X-ray diagnosis in any case.

The test was used also on 19 patients who came to postmortem. In all these cases, the interval between the date of the test and the date of the autopsy was from two weeks to two months. It was found that the test coincided with the postmortem findings in 14 cases (74 per cent) and failed to agree in 5 cases (26 per cent). Interestingly enough, the percentage of error here (26 per cent) was the same as the percentage of error in the above group of 230 cases.

STOOL EXAMINATION

Every patient with pulmonary tuberculosis with symptoms referable to his gastrointestinal tract has three stool examinations on consecutive days after being on a meat-free and fish-free diet for three days. This always precedes the roentgenological study of the intestinal tract. The reason for this is that the roentgenological signs of intestinal tuberculosis are merely indirect spastic phenomena encountered in any ulcerative lesion and all efforts must be made to rule out other possibilities (that is, amoebiasis) before making a diagnosis of intestinal tuberculosis. A total of 474 stool examinations were carefully done on 158 patients; 79 of these patients were found to have roentgenological evidence of intestinal tuberculosis, while the other 79 were found to be free of intestinal disease. Occult blood (benzidine test) was found in the intestinal cases almost twice as frequently as in the negative cases, 60 per cent of the positive cases and 35 per cent of the negative cases giving a positive test. Cellular exudates (pus cells, lymphocytes) on the other hand were found with almost equal frequency in both groups (56 per cent of the positive cases and 59 per cent of the negative cases). No attempt was made to grade the number of cells found; an occasional pus cell in a stool examination was called positive just as were those containing a larger number. Berkovitz (13), from a careful study of cellular exudates of 1,123 individuals, concluded that where there was a diseased bowel cellular exudates would be found in the stools and, conversely, no cells would be found in

cases whose bowel was normal. We did not make any attempt to rule out the presence of any nonulcerating form of colitis in this study. Our main interest was centered on differentiating a tuberculous enteritis from a so-called normal bowel by means of roentgenographic studies.

CONCLUSIONS

1. Woldman's phenolphthalein test is of no aid in proving the presence of intestinal tuberculosis.

2. Stool examinations are of no help in proving the presence of tuberculous ulcerations in the intestinal tract. These examinations are important, however, in ruling out other diseases which give a similar roentgenological picture and should be done in every case.

3. The diagnosis of intestinal tuberculosis can be made on the basis of the following findings:

(*a*) Pulmonary tuberculosis with a positive sputum (or a history of a positive sputum).
(*b*) Symptoms referable to the gastrointestinal tract which we have found in 96.5 per cent of patients with intestinal tuberculosis.
(*c*) Roentgenological studies of the intestinal tract showing the characteristic ileocaecal spastic filling defect.

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INFLUENCE OF POSTURE ON THE INTRAPLEURAL PRESSURE IN ARTIFICIAL PNEUMOTHORAX[1]

SAMUEL COHEN

The intrapleural pressure under ordinary conditions is always subatmospheric or negative. This negative pressure is greater during inspiration and reduced during expiration. During quiet inspiration in humans it amounts to about −6.0 cm. of water and during expiration it is reduced to about −2.5 cm. of water; in the midposition it is approximately 4.5 cm. When these respiratory movements are forced the intrapleural pressure, of course, may be tremendously increased or decreased in the respective phase of respiration. These fluctuations in pressure exert, as is well known, an influence upon other structures in the thorax, particularly upon the filling and emptying of the thin-walled veins.

Carson (1820) (1) was apparently the first to measure the "resilient property" of the lungs in animals by connecting a water manometer to the windpipe and observing the pressure change after a bilateral open pneumothorax had been induced. Powell (1868) (2) was the first to record positive intrapleural pressure in a valvular pneumothorax ("the air pressure was found to be equal to four inches of water"). This was done on the cadaver of a patient who died of pulmonary tuberculosis. The first successful effort to measure the intrapleural tension in normal living persons was evidently made by Aron (1891) (3). Readings (a glycerine manometer connected with a syphon drain was used) were taken during both phases of respiration (the time interval in seconds of inspiration and expiration was also noted) and in the lying and sitting positions. In recent years, Christie and McIntosh (1934) (4) particularly have emphasized the variations in distensibility of the lungs with changes in posture. They noted that the change from the recumbent to the sitting position resulted in a decrease of the intrapleural pressure by about 2.5 cm. of water. The change was accompanied by an increase of several hundred cubic centimetres of air in the lungs. Prinzmetal and Kountz (1934) (5) took the intrapleural pressures in both the recumbent

[1] From the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, Jersey City, New Jersey.

and upright positions in 13 individuals, 7 of whom were orthopnoeic and 6 were not. In all cases the intrapleural pressure was less negative or more positive in the former position. The shift was greater in patients with orthopnoea than in the control group.

PRESENT STUDY

Material: This study was undertaken with the purpose of determining the influence of posture on the intrapleural pressure of patients receiving artificial pneumothorax. One hundred and ten cases who were receiving this therapy for pulmonary tuberculosis were studied. Their ages ranged from thirteen to forty-nine years. Ninety-eight had a unilateral and 12 a bilateral pneumothorax. The duration of collapse therapy varied from two weeks to thirty-two months and the degree of pulmonary compression from about 15 to 90 per cent.

Procedure: With the needle in the pleural cavity at the same site (in almost all of these cases the site was the third anterior interspace in the anterior or midaxillary line), readings were recorded with the patients in the following positions: flat on back or supine, lateral recumbent (pneumothorax side up), sitting. The patient was instructed to breathe naturally and the accepted reading was reached when three consecutive readings at the end of inspiration and expiration were the same or as nearly the same as could be reasonably expected. The Bethune pneumothorax apparatus was used and the intrapleural findings expressed in centimetres of water (the change was measured in only one arm of the manometer). A kymograph attached to the pneumothorax machine can be utilized to obtain permanent visual records (figure 1). The arrangement is simple and applicable for teaching purposes.

RESULTS AND CONCLUSIONS

1. The intrapleural pressures were consistently found to be:

(*a*) Most subatmospheric in the lateral recumbent position.
(*b*) Less subatmospheric in the sitting position.
(*c*) Least subatmospheric or most positive in the supine position.

2. The intrapleural variations were as follows:

(*a*) Differences between readings in lateral recumbent and supine posture:

	At end of inspiration in cm. of water	*At end of expiration in cm. of water*
Minimum difference	0	0.5
Maximum difference	9.0	12.0
Average difference	2.7	4.3

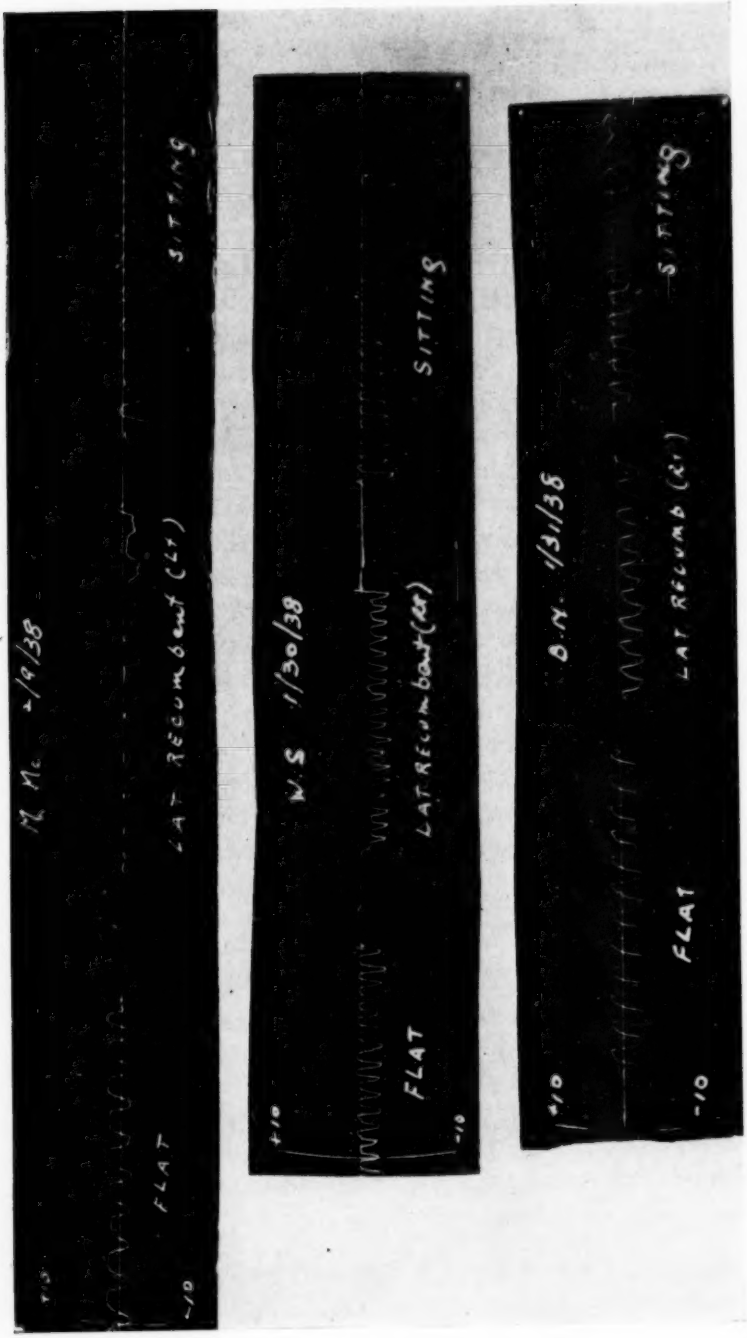
M.M. 1/9/38
LAT. RECUMBENT (L.)
SITTING
+10
FLAT
-10
W.S. 1/30/38
LAT. RECUMBENT (R.)
SITTING
+10
FLAT
-10
D.N. 1/31/38
LAT. RECUMB. (R.)
SITTING
+10
FLAT
-10

FIG. 1

(*b*) Differences between readings in lateral recumbent and sitting-up posture:

	At end of inspiration in cm. of water	*At end of expiration in cm. of water*
Minimum difference	0	0
Maximum difference	7.0	10.0
Average difference	1.5	2.9

(*c*) Differences between readings in sitting-up and supine posture:

	At end of inspiration in cm. of water	*At end of expiration in cm. of water*
Minimum difference	0	0
Maximum difference	7.0	10.0
Average difference	1.5	1.8

It is noted that in all three instances, the greatest average variation was at the end of expiration.

3. In the 12 cases with bilateral pneumothorax, simultaneous pressure readings were taken on both sides. As mentioned above, the intrapleural pressure is most subatmospheric in the lateral recumbent position. This is true on the pneumothorax side that is uppermost. The simultaneous reading on the dependent pneumothorax side definitely becomes more positive due to diminished respiratory movement on this side and the displacement of the mediastinum toward it.

4. In a recent excellent article, McMichael and McGibbon (1939) (6) reported on the postural changes in pulmonary volume. They observed the following physiological changes in the supine position which undoubtedly explain why intrapleural pressures are least subatmospheric in this position: (*a*) a decrease of total lung volume (the average reduction was 340 cc. in the group of 25 patients studied)—this is believed due to increased congestion of the pulmonary vessels in the supine position; (*b*) a decrease in functional residual air (average 780 cc.)—this is caused by the upward displacement of the diaphragm by the abdominal organs which reduces the air volume in the lungs; (*c*) a decrease in residual air (average 150 cc.); (*d*) a decrease in vital capacity (average 190 cc.).

SUMMARY

The intrapleural pressure under ordinary circumstances is a subatmospheric pressure.

A study of 112 cases of artificial pneumothorax (12 of which were bilateral) has been undertaken in order to determine the fluctuations in intrapleural pressure during quiet respiration with changes in posture of

the patient. Readings were obtained with the patient in the following positions: (*a*) supine, (*b*) lateral recumbent, and (*c*) sitting. The findings have been presented briefly. The attachment of a kymograph to the pneumothorax apparatus makes available permanent registration of the pressure readings.

Physiological changes in pulmonary volume dependent on postural changes are associated with variations in the intrapleural pressure.

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CHEMOTHERAPY OF EXPERIMENTAL TUBERCULOSIS[1]

H. HARRIS PERLMAN, HERMAN BROWN AND GEORGE W. RAIZISS

With the assistance of Miss Anna Rule

For many years men have been seeking to discover a chemotherapeutic agent destructive of the tubercle bacillus *in vivo*. The resulting voluminous literature is proof of the enthusiastic endeavors of the research workers in this field. However, it is not the purpose of this paper to review in any great detail that literature, especially since a brief review of such contributions is already available in the excellent treatise of Wells and Long (1); rather it is to present certain researches that have been undertaken recently in the hope of adding to the work accomplished previously in that field.

REVIEW OF THE LITERATURE

Volatile oils (etheral oils): Baldwin, Petroff and Gardner (2) observed that the vapors of volatile oils, such as peppermint, clove, eucalyptus, restrain the growth of cultures of tubercle bacilli, but they presented no data of animal experiments.

Cinnamic acid, a constituent of balsam of peru, has been studied by several investigators. As early as 1893 (3) Landerer injected intravenously an alkaline 5 per cent cinnamylic acid emulsion (with egg yolk) in 18 individuals afflicted with internal (visceral) tuberculosis. Somewhat earlier, Landerer had used balsam of peru but he found his results with cinnamic acid were more striking. Of these, he said, "In the treatment of surgical cases of tuberculosis cinnamylic acid is in its effect equal to iodoform. While admitting the fact that many physicians declare intravenous injection to cinnamylic acid emulsion as a dangerous process there are no unpleasantness nor any threatening conditions in applying this form of treatment provided the doses administered are kept within certain limits." Landerer concluded by expressing his faith in this form of medication and hoping that it would find wide application. Later he employed sodium cinnamate or ketol, for which he claimed better therapeutic results than for the emulsion. Other advantages of the

[1] From the Research Institute of Cutaneous Medicine, Philadelphia, Pennsylvania.

sodium salt were its solubility to the extent of 5 per cent, its nontoxicity, its ease of sterilization and its availability in pure form; yet, after many trials, sodium cinnamate, too, was discarded as unsatisfactory, because it proved therapeutically inefficient.

Jacobson (4) studied a derivative of cinnamic acid which has a cinnamic acid radical and at the same time possesses an alcoholic action, namely, cinnamic ether of ethyl alcohol or ethyl cinnamic ether. Jacobson carried out his researches both *in vitro* and *in vivo*. *In vitro* he studied the development of Koch's bacillus on glycerine-potato medium to which he added ethyl cinnamic ether. His conclusion was, after deductions from weight experiments, that 0.001 mg. of ethyl cinnamic ether hindered the development of 0.002 mg. of culture of Koch bacillus. *In vivo*, Jacobson studied the thermic reaction brought about by tuberculin upon the tuberculous organisms. Using either method, he proved that the thermic action provoked in tuberculous guinea pigs by the injection of pure tuberculin is more intense and of longer duration than the thermic reaction produced in like guinea pigs by a like quantity of tuberculin mixed with ethyl cinnamic ether. He found also that ethyl cinnamic ether, injected subcutaneously into tuberculous guinea pigs, brought about a passing leucocytosis; the same quantities of ethyl-cinnamic ether injected into nontuberculous guinea pigs caused no leucocytic reaction.

In a series of notes addressed to the Société de Biologie, Jacobson (5) indicated the reasons which led him to try benzyl-cinnamic ether. With it he obtained favorable results in the treatment of cutaneous tuberculosis which were confirmed by Darier, Jean-Selme, Mitchnick, Froitsard and by others at three congresses of dermatology held in the French language (1922, Paris; 1924, Strasbourg; 1926, Brussels), particularly by Vignes and Fournies. Benzyl-cinnamic ether is said to have been used efficaciously in the treatment of tuberculous lymph nodes, genital tuberculosis, tuberculosis of the mucous membrane, tuberculosis of the larynx and also in the treatment of tuberculous cysts. However, in the treatment of pulmonary tuberculosis, Jacobson admitted that his studies and observations were of short duration, although he spoke highly in favor of the treatment.

Corper *et al.* (6) elaborated on Jacobson's studies with sodium-cinnamate. Gekler (6) from preliminary studies felt it possessed possibilities as a tuberculocide because of its low toxicity. He found that repurified sodium cinnamate in concentrations of 2 per cent has no tuberculocidal action within three days, but is distinctly inhibitory to the human

tubercle bacillus in 5 per cent glycerine-agar in a concentration of 0.05 per cent; while in rabbit-blood medium, both fresh and inspissated, it is inhibitory only in a concentration of about 0.2 per cent. However, he found that sodium cinnamate cannot be used as an inhibitory agent in tuberculosis over a prolonged period of time because of its haemolytic action.

GENERAL PROCEDURE

In line with the foregoing researches, in the present studies an attempt was made to determine the effect, in guinea pigs infected with a virulent strain of bovine tubercle bacilli (Ravenel), of certain chemical compounds, namely, thymol, menthol, cinnamic aldehyde and eucalyptol which represent the solid portions of volatile (aromatic) oils known chemically as stearoptens. They were employed either alone or injected in physical combination, dissolved in sterile peanut oil in strengths of 2.5 to 10 per cent. Similar studies were carried out with alkyl phenols and their halogenated derivatives, the latter group of compounds including monochloro-iso-amyl-thymol, monobromo (1 ethyl-propyl-m-cresol) 1-ethyl propyl-beta-naphthol. Lastly, four amino-acids, namely, cystine, asparagin, glycine and alanine, were administered subcutaneously to tuberculous guinea pigs in 10 per cent strength in sterile distilled water in order to determine their effect in preventing loss in body-weight.

The series of investigations were carried out from the following standpoints of inquiry: (*1*) The effect of the therapeutic remedy upon nutrition, as gauged by gain or loss in weight in the animals studied. It is to be noted as a precaution against miscalculation that the loss or gain in weight of guinea pigs infected with a virulent strain of tubercle bacilli represents a combination of two factors, namely, the age of the animal and the effect of the infection. Accordingly, since most of the guinea pigs in the present studies were quite young, it is to be understood that their natural growth may have had more effect than the tuberculous infection, and thus may account for a net gain in weight, which otherwise would not have occurred.

(*2*) Evidence of infection with tuberculosis as noted upon weekly examination, by (*a*) a gradual increase in the size of the right and left chains of inguinal lymph nodes, (*b*) by observing the gross lesions characteristic of tuberculous infection in the lymphatic structures and other organs, such as the spleen, liver, lungs, pleural and peritoneal cavities, at the time of autopsy.

(*3*) Longevity of treated animals compared to that of untreated but similarly infected controls.

(*4*) Microscopical evidence by identification of tubercle bacilli in stained smears of various organs infected with tuberculosis. Further, an attempt was made to evaluate the severity or mildness of the infection by observing the numbers of tubercle bacilli found in the smears.

EFFECT OF THYMOL, MENTHOL, AND THYMOL AND MENTHOL COMBINED

Four series of 4 guinea pigs each were inoculated subcutaneously in the left groin with 0.2 cc. of saline containing 0.000,05 mg. of tubercle bacillus (Ravenel). Three days later the first series of animals received intramuscularly, and thereafter at five day intervals, alternately in the right and left thighs, 5 per cent thymol in peanut oil in doses of 0.4 cc. per kilogram weight; the second series of animals, 5 per cent menthol in peanut oil in similar dosage; the third series, 5 per cent thymol and 5 per cent menthol in dosage of 0.2 cc. per kilogram body weight. The fourth or control group received peanut oil without any medication in dosage of 0.4 cc. per kilogram of body weight. All animals were weighed once every five days, at which time they were examined to determine the size of the inguinal lymph nodes. A rest period of two weeks' duration was instituted after the fourth injection of both the medicated and nonmedicated oil because of the induration of the thigh muscles that resulted from repeated injections.

As a result of the foregoing procedure, all treated animals lost weight; the loss was only slightly less for the treated animals than for the untreated animals, the average loss for the three treated groups being 62.3 g., as compared to 71 g. for the control animals.

The three groups of treated animals lived ten days longer (average ninety-two days) than the control groups (average eighty-two days).

Milder infections occurred in the 5 per cent thymol and the combined 5 per cent thymol and 5 per cent menthol groups than in the animals of the 5 per cent menthol and the control groups.

Accordingly, it is inferred that 5 per cent thymol or a combination of 5 per cent thymol and 5 per cent menthol was responsible for the milder types of infection in the animals so treated.

EFFECT OF THYMOL AND MENTHOL COMBINED AND OF CINNAMIC ALDEHYDE AND EUCALYPTOL

The encouraging results with 5 per cent thymol and 5 per cent menthol in the previous study suggested the further use of both these compounds

in combination, but in 2.5 per cent strength. Accordingly, three series of 4 guinea pigs each were treated in the manner already described; the first series with 2.5 per cent thymol and 2.5 per cent menthol; the second series with 5 per cent cinnamic aldehyde; the third series with 5 per cent eucalyptol. Again, the compounds were dissolved in peanut oil and administered in dose of 0.4 cc. per kilogram of body weight.

Two treated groups of guinea pigs gained weight, the greater gain being made by the 5 per cent eucalyptol group, while one group lost weight.

There was no appreciable difference in the survival time of the treated animals, as compared to that of the controls. The longest duration of life was found in the 5 per cent cinnamic aldehyde group, but the animals in that group lived only seven days longer than the controls.

The most encouraging results, in order of importance as determined by the examination of smears for tubercle bacilli, were found in the following groups: (*1*) 5 per cent eucalyptol, (*2*) 2.5 per cent thymol and 2.5 menthol, (*3*) 5 per cent cinnamic aldehyde. Accordingly, from the foregoing study it is inferred that 2.5 per cent thymol and 2.5 per cent menthol, also 5 per cent cinnamic aldehyde and particularly 5 per cent eucalyptol, probably play some part in rendering infection with tubercle bacilli milder in guinea pigs.

EFFECTS OF COMPOUNDS SINGLY AND COMBINED IN 10 PER CENT STRENGTH

This experiment was in part a repetition of the first study, except that the thymol and menthol were doubled to 10 per cent. The procedure was also followed with thymol and menthol combined in 10 per cent strength. Because of the encouraging results observed with eucalyptol, that compound was also used in 10 per cent alone in two separate experiments and in combination with 10 per cent menthol and in combination with 10 per cent thymol.

Seven series of 5 guinea pigs each were inoculated and treated according to the uniform procedure of these experiments.

Treatment and survival times were as follows:

	days
Group I: 10 per cent eucalyptol	53
Group II: 10 per cent thymol	37
Group III: 10 per cent menthol	40
Group IV: 10 per cent eucalyptol and 10 per cent thymol	48
Group V: 10 per cent eucalyptol and 10 per cent menthol	59
Group VI: 10 per cent thymol and 10 per cent menthol	48
Group VII: Controls	23

Two groups of animals, both treated, gained weight:

	grams
10 per cent eucalyptol and 10 per cent thymol	29
10 per cent eucalyptol	8

An interesting observation was afforded by a study of the size of the inguinal lymph nodes. In animals treated with 10 per cent eucalyptol, 10 per cent thymol or 10 per cent menthol, the lymph nodes, both at the site of infection and upon the opposite side, either remained normal or were only slightly enlarged. Likewise, animals treated with combinations showed only slight enlargement of the nodes; in contrast, in the majority of the controls the nodes were very much enlarged.

All organs showed evidence of tuberculosis. The lesions consisted of definite enlargement of the spleen, although in a few instances among the 10 per cent eucalyptol-treated group, the spleens appeared normal upon gross examination. Necrotic lesions were found in most of the spleens and livers. The lungs of one of the 10 per cent menthol-treated animals showed abscess formation but among the controls were noted pneumonia and pleurisy.

In smears from the organs, the most numerous negative findings were found in the 10 per cent thymol group (16 negative, 4 positive). The next largest number of negative smears was among the 10 per cent eucalyptol group (8 negative, 12 positive); and the same for the 10 per cent menthol group.

Because of the significant increase in longevity shown by the 10 per cent eucalyptol group, and the combined 10 per cent eucalyptol and 10 per cent menthol group, it seemed worth while to continue experiments with these medications. Accordingly, two series of 6 guinea pigs each were inoculated and treated according to the procedure already detailed: the first series with 10 per cent eucalyptol in peanut oil; the second series with 10 per cent eucalyptol and 10 per cent menthol in the same medium in a dosage of 100 mg. per kilo of body weight. Together with these a series of 13 controls was employed.

Generally, the results of these two series were far less striking than those of the preceding series.

All animals gained weight; the 10 per cent eucalyptol treated, 8 g.; the 10 per cent eucalyptol and 10 per cent menthol treated, 1 g. However, the controls gained 13 g.

All animals, both treated and untreated, showed slightly enlarged inguinal lymph nodes. Examination of the organs of the treated groups

showed no demonstrable differences from those of the controls; all gave gross evidence of tuberculosis. Smears showed no appreciable differences between treated and untreated animals.

From the foregoing results it is inferred that certain chemical compounds administered to guinea pigs, either alone or in combination, exert some influence upon the severity of the infection so that it is rendered milder in treated than in untreated groups of animals similarly infected.

EFFECT OF VARIOUS ALKYL PHENOLS AND THEIR HALOGENATED DERIVATIVES UPON EXPERIMENTAL TUBERCULOSIS IN GUINEA PIGS

Nine series of guinea pigs were inoculated and treated in the usual manner of these experiments. The compounds administered were prepared in 5 per cent solutions of sterile olive oil, and each was given in dosage of 1.0 cc. per kilogram of weight. The following compounds were given to infected guinea pigs:

CHEMICAL COMPOUNDS	NUMBER OF GUINEA PIGS
Part I	
Monochloro-iso-amyl-thymol	5
Monobromo (1-ethyl-propyl)-m-cresol	5
Iso-amyl-thymol	5
Menthyl-thymol	5
Menthyl-thymol	5
Controls	7
Part II	
Monochloro-(1-ethyl-propyl)-p-cresol	4
(1-ethyl-propyl)-beta-naphthol	4
Controls	3

All treated animals lost weight. The greatest loss was incurred by the monochloro-iso-amyl-thymol treated group (75 g.); the smallest loss occurred in the iso-amyl-thymol group (6 g.). The control group in part II gained 27 g.

As compared with longevity in the control group of guinea pigs, no startling difference was observed in any of the groups of treated pigs. The mean duration of life for the control group of animals in part I was thirty-one days, while the mean longevity of the treated groups of guinea pigs varied from twenty-nine to thirty-three days. All treated and

untreated animals died from tuberculosis. In part II, the mean duration of life was nineteen days. One group of treated guinea pigs lived 20 days and another twenty-three days. All animals in the treated and control groups died.

The lymph nodes of all treated animals, as well as those of the control group, showed only slight enlargement. All animals showed unmistakable signs of tuberculosis. The spleens were enlarged and, for the most part, spotted. The livers and lungs of all animals were spotted with tuberculous lesions. Smears of the spleen, liver and lung showed tubercle bacilli.

Certain alkyl phenols and their halogenated derivatives failed to prevent loss of weight, to increase longevity or prevent the spread of disease in tuberculous guinea pigs.

THE RESPONSE OF WEIGHT LOSS TO CERTAIN AMINO-ACIDS IN EXPERIMENTAL TUBERCULOSIS

The object of this study was to determine whether amino-acids had any effect in preventing loss of weight, such as is incident to the progress of tuberculous infection in guinea pigs. The same procedure for studying the effect of the amino-acids upon tuberculosis in guinea pigs was employed in this study as was carried out with the various agents in the foregoing investigation.

Four series of 3 guinea pigs each received an aqueous sterile 10 per cent solution of the following amino-acids: cystine, asparagin, glycine and alanine. A fifth series of 13 guinea pigs served as controls.

With the exception of cystine, the subcutaneous injection of certain amino-acids, namely, asparagin, glycine, and alanine, in 10 per cent aqueous solution, repeatedly administered to guinea pigs infected with tubercle bacilli, failed to prevent loss in weight to any appreciable degree.

There was no marked difference in the longevity of guinea pigs treated with the amino-acids as compared with that of the control group.

The acids showed no demonstrable effect on the severity of tuberculous infection in guinea pigs. At autopsy all animals had characteristic lesions of tuberculosis, confirmed by identifying the tubercle bacillus in smears from various organs.

SUMMARY

1. The subcutaneous administration of 5 per cent thymol, menthol, eucalyptol and cinnamic aldehyde to guinea pigs, infected with a virulent

strain of bovine tubercle bacilli (Ravenel), rendered infection milder as compared to that in similarly infected untreated animals. The longevity of the treated animals was appreciably increased as compared to that of the control groups of pigs, and there was in many instances a failure to recover tubercle bacilli by an examination of stained smears from the various organs.

2. Encouraging but less striking results were obtained with guinea pigs when thymol and menthol were administered separately in 10 per cent solutions.

3. Moderate to severe tuberculosis was observed in guinea pigs treated with 10 per cent eucalyptol, 10 per cent each of eucalyptol and menthol combined, 10 per cent each of thymol and menthol combined, and 10 per cent each of eucalyptol and thymol combined. In these experiments it was found that longevity was twice, and often two and a half times, as long as that of control groups.

4. The alkyl phenols and their halogenated derivatives had no effect in mitigating the infection, in preventing a loss in weight or in increasing longevity, as compared to that of untreated infected animals. On the contrary, some of the severest lesions were found in the treated animals of this group.

5. The amino-acids, cystine, asparagin, glycine and alanine, failed to prevent loss of weight, to increase longevity, and to modify the course of the infection in guinea pigs injected with a virulent strain of tubercle bacilli.

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SPONTANEOUS CLOSURE OF TUBERCULOUS CAVITIES[1,2]

A Roentgenological Study

E. ROBERT WIESE

The work here presented was undertaken to determine, as nearly as possible, the incidence of spontaneous closure of tuberculous cavities of the lungs in patients in White Haven Sanatorium.

We have made extensive study of the reports and of the X-ray films of 1,000 patients. These 1,000 cases comprised the following:

Pulmonary tuberculosis with cavitation	597
Pulmonary tuberculosis without cavitation	129
Normal lungs and healed lesions	99
Anthracosilicosis	61
Anthracosilicosis and tuberculosis	88
Other conditions:	
Pleuritis, bronchiectasis, abscess, neoplasms, cysts of the lungs, chronic congestion, Hodgkins disease	26

From the 597 cases of pulmonary tuberculosis with cavitation the following were deducted because they were not suitable for our study:

165 patients who died while in the Sanatorium
184 patients subjected to some form of collapse therapy
123 cases having but one film and hopeless cases

This left 125 cases of pulmonary tuberculosis with cavitation that were suitable for our study.

These 125 were not selected, but were for the most part at least rejected cases, as they had been considered not suitable for collapse therapy. Upon study we found among them 20 instances where closure took place spontaneously with no other treatment than that of strict bed-rest. For the purposes of this paper a cavity was considered closed when the outlines of the walls or the area of rarefaction could no longer be seen roentgenologically and marked improvement in the condition of the patient was noted clinically. While these patients were never considered

[1] From the White Haven Sanatorium, White Haven, Pennsylvania.

[2] Summary of a paper read before the Laennec Society of Philadelphia, April 9, 1940.

hopeless, none was ever looked upon as promising of good results. The essential features may be summed up as in tables 1 and 2.

As a rule the cavities were regular in outline; there were but 3 exceptions. In all instances the walls were thin. The method of closure varied; it was quite the usual thing to see them gradually becoming smaller when successive films were compared, until one could see only a small fibrotic deposit or several strands of fibrotic tissue, not infrequently stellate in outline, in place of the former cavity. In one instance nothing remained visible to indicate the site of the lesion. In another case the

TABLE 1

SEX	NUMBER	OLDEST	YOUNGEST	SPUTUM				CAVITY	
				On admission		On discharge			
				Positive	Negative	Positive	Negative	Right	Left
Males	10	48	20	10		3	7	8	2
Females	10	33	20	10			10	2	8

TABLE 2

SIZE	NUMBER	CLOSURE TIME	CONDITION OF PATIENT MARCH, 1940	CAVITY HAS BEEN CLOSED MARCH, 1940
		months		
Up to 2 cm.	4	2 to 23	4 living and well	8 months to 6 years 10 months
2 to 3 cm.	5	3 to 22	1 unknown. 4 living and well	1 year to 3 years 9 months
3 to 4 cm.	7	3 to 67	7 living and well	6 months to 6 years 5 months
Cavity nests	4	6 to 16	4 living and well	2 years 3 months to 3 years 9 months

area occupied by the cavity became dense and resembled ground glass, an appearance indicative of atelectasis; this gradually diminished in size and eventually left behind a scar.

The above is but a summary of the cases in which cavities closed spontaneously on bed-rest only. Under no circumstances do we wish to give the impression that 16 per cent of all cavities will close spontaneously on bed-rest. Our search however has shown that in this particular group 16 per cent of our cavity cases closed spontaneously where collapse therapy was not employed in patients who were not hopelessly ill.

PRESENT STATUS OF THE TUBERCULIN PATCH TEST[1, 2]

CAMILLE KERESZTURI

The tuberculin test is one of the most important adjuncts in the control of tuberculosis. Best known among the tuberculin tests done by injection are the subcutaneous test of Koch, the percutaneous test of Pirquet and the intracutaneous test of Mantoux. The last has stood best the test of time.

In spite of the satisfactory character of the Mantoux test, there has been a continuous search for a tuberculin test which eliminates the process of injection. In other words, a test has been sought which requires mere contact between the patient's skin and Old Tuberculin. Among the contact tests used in Europe the innunction method of Moro and the plaster ointment test of Malmberg and Fromm are the best known. Both are regarded as inferior to the Mantoux or Pirquet tests.

In the United States the patch tuberculin test of Vollmer, first described in 1937, has aroused considerable interest. The present study and review of reported findings was undertaken in response to this interest and with a view to assessing the value of the simplified contact test.

TECHNIQUE OF THE PATCH TEST OF VOLLMER

"Thin filter paper is saturated with tuberculin, produced on a synthetic medium, dried, cut into squares of 1 x 1 cm. and placed on adhesive tape 1 x 3 inches in size. Each strip of tape contains two tuberculin squares placed on each side of a control square; the latter consisting of filter paper saturated with glycerin broth. The dried tuberculin contained in the filter paper must be protected from excessive moisture before use. Through the natural moisture of the skin (*perspiatio insensibilis*) the tuberculin is dissolved and absorbed sufficiently to render reliable cutaneous reaction."

[1] From the New York Institute for the Education of the Blind, Department of Pediatrics, Columbia University, New York City.

[2] This study was made possible through the interested coöperation of Dr. William Barcley Parsons, one of the trustees of the New York Institute for the Education of the Blind, of Dr. Merle E. Frampton, the Principal, and of Mrs. K. D. Longsdorf, R.N., the nurse of the school. Dr. Ashley Weech from Babies Hospital was kind enough to read the manuscript and give helpful criticism and suggestions.

Doctor Vollmer and the Lederle Laboratories are recommending the following method for making the patch test:

"An area of skin over the sternum, along the upper spine, or on the inner side of the forearm, is thoroughly cleansed and defatted with acetone, (a small pledget of fresh cotton for each patient). Hairy areas should be avoided. In the case of children the sternum is better. In the case of infants it may be preferable (in order to avoid accidental or deliberate premature removal of the adhesive tape) to place the test on the back, along the upper spine. The entire strip of adhesive, after the removal of the crinolin, is applied carefully to the cleansed area under pressure with the warm palm of the hand. Care should be taken to keep the paper squares near the central line of the adhesive tape. If they become misplaced toward the margin of the tape, they may not be properly sealed in.

"Leave the tape holding the patches in contact undisturbed, for forty-eight hours; then remove the tape. Make reading of the test forty-eight hours after removal of the tape.

"The removal of the tape, even if replaced at once, during the forty-eight hour period of contact, may result in fewer positive reactions. Bathing or wetting of the affected area should be avoided during the forty-eight hour period.

"While some positive reactions may be read immediately after the removal of the tape, it is recommended that reading be made forty-eight hours afterward, when early reactions will not have disappeared and some late reactions will have developed. The patient should be advised to inform his physician if later reactions occur."

The interpretation of the reaction is described in the articles of Vollmer and Goldberger (9) and in the circular of the Lederle Laboratories as follows:

"A positive reaction appears as sharply circumscribed, infiltrated and reddened squares with lichenoid-follicular elevations. The central control square appears pale. Individuals with sensitive skin occasionally show a nonspecific irritation due to the adhesive, which does not interfere with the reading of the reaction, as in the case of a negative reaction the areas covered by the tuberculin squares appear paler than the surrounding skin and in the case of positive reactions the square areas appear of a more intense red. Quantitative degrees can be differentiated if desired as follows:

One plus—A few lichenoid efflorescences.

Two plus—Lichenoid-follicular eruptions assembled in clear-cut square.

Three plus—Confluent eruption with marked induration and elevation in square form.

Four plus—Spread of the cutaneous reaction beyond the square area or blister formation."

SURVEY OF THE LITERATURE OF THE PATCH TEST OF VOLLMER

Up to the present date there exist 19 publications dealing with a total of 8,594 subjects in whom the tuberculin patch test of Vollmer has been compared with other accepted standardized tuberculin tests. For various reasons all of these findings cannot be pooled together and evaluated collectively. In some reports the standardized control has been the Pirquet test; in others it has been the Mantoux test. When the Mantoux test was employed the dosage has covered a wide range; 0.1, 0.1, 1.0 and even 10.0 mg. Old Tuberculin have been used. Some investigators have preferred Purified Protein Derivative to Old Tuberculin. Some have considered a reaction to be positive only when induration reached a diameter of 10 mm.; others have been satisfied with an infiltrative reaction 5 mm. in diameter. Moreover, some investigators have dealt with children and others with adults. Finally, and perhaps of primary importance for our purpose of appraisal, some studies were carried out in institutions in which presumably all of the subjects were infected with tuberculosis while others were made on populations with a relatively low incidence of infection.

In reviewing these heterogeneous data it is clear that answers to two questions must be sought. Both questions concern the reliability of the patch test. The first deals with groups of infected subjects and asks what percentage of the cases will be missed by failure to show a positive test. The second deals with groups of uninfected subjects and asks what percentage will be improperly diagnosed as infected by the occurrence of false positive reactions. Unfortunately, a completely satisfactory answer to these questions cannot be attained since there is no way of distinguishing in the available data between infected and uninfected subjects except in terms of the control tuberculin test. The situation is further complicated by the circumstance that some authors have not distinguished between the negative reaction in an infected subject and the possibly false positive reaction; in these articles the percentage discrepancy or failure of conformity between the two tests is reported without distinction between the two types of unreliable tests. Indeed, in some papers discrepancies in individual patients are not recorded at all, the author merely giving the total number of positive and negative reactions to the two tests.

For the reasons cited above it has seemed wise to utilize for general appraisal data from only 9 of the 19 reports in the literature. These data deal with a total of 4,162 tests. In all of them the control test was performed by the Mantoux technique in dosages which were always increased to 1.0 mg. or more of Old Tuberculin or to a biologically equivalent amount of Purified Protein Derivative.

The summary of these data, given in table 1, was prepared on the assumption that the control tests were adequate for separating infected and noninfected subjects. Because the assumption cannot be accepted without reservation, interpretation must allow for some error in the accuracy of the separation. The uniform arrangement of the data in the table was made to fit the purpose of critical review; the summaries are not in the form in which they were presented by the authors. For each article the total number of tests is given together with the distribution of the results among the four possible categories, namely, both tests negative, both tests positive, control test positive and patch test negative, control test negative and patch test positive. Computations presented in the last two columns give the information concerning the percentage of discrepancy between the two tests. The method of computing these percentages, outlined in principle above, can be illustrated by the 169 tests of Vollmer in 1938. Here the control test indicated that 166 of the subjects were infected and, of these, 165 were identified by the patch test and one was not. Failure of the patch test to identify infection is therefore listed as one in 166, or approximately 0.5 per cent. Conversely the control test indicated that 3 of the 169 subjects were not infected and, of these, one gave a positive reaction to the patch test. The false positive reactions are therefore listed as one in 3, or 33 per cent. From the illustration it will be clear that the percentages have little meaning in reports where only a few cases are involved, also that the designation "false positive" should not be taken too literally since such a result will be tabulated when the control test has failed to identify an infection which led to a legitimately positive patch test. The totals for all authors show 1,856 control-positive subjects with failure of identification by the patch test in 270, or 15 per cent, and 2,306 control-negative subjects with false positive reactions in 78, or 3 per cent. Although there is no good reason for eliminating the results of individual investigators it is of interest to note that 67 of the total of 78 false positive reactions were recorded by Pearse. If these data are removed from the totals, the percentage of false positives falls to 0.6 per cent. Conversely 225 of the

270 instances in which the patch test failed to identify infection were recorded by Peck. If his data are removed from the totals the failures

TABLE 1

Summary of the literature of the tuberculin patch test of Vollmer

AUTHOR	TOTAL NUMBER OF CASES	CONTROL TUBERCULIN	BOTH TESTS NEGATIVE	BOTH TESTS POSITIVE	CONTROL POSITIVE, PATCH NEGATIVE	CONTROL NEGATIVE, PATCH POSITIVE	PER CENT FALSE NEGATIVE PATCH TEST	PER CENT FALSE POSITIVE PATCH TEST
Vollmer 1938	169	PPD	2	165	1	1	1/166 0.5%	1/3 33%
Vollmer 1938	118	OT	106	10	—	2	—	2/108 2%
Hart	536	OT	436	97	3	—	3/100 3%	—
Leonidoff	189	PPD	2	185	2	—	2/187 1%	—
Vollmer 1939	251	OT PPD	4	245	1	1	1/246 0.4%	1/5 20%
Peck	880	PPD	561	94	225	—	225/319 71%	—
Hughes	100	PPD	—	89	11	—	11/100 11%	—
Pearse	712	PPD	492	132	21	67	21/153 14%	67/559 12%
Vollmer 1940	667	OT	616	41	4	6	4/45 9%	6/622 1%
Vollmer 1940	540	PPD OT	9	528	2	1	2/530 0.4%	1/10 10%
Totals.....	4,162	OT PPD	2,228	1,586	270	78	270/1,856 15%	78/2,306 3%

Note: The control test consisted of 0.01 to 10.0 mg. Old Tuberculin intracutaneously or its equivalent in PPD.

become 3 per cent instead of 15 per cent. Comment on these discrepancies of observation will be reserved until the results of our own experience have been presented.

OUR EXPERIENCE WITH THE PATCH TEST

In 1938 and again in 1940, we had an opportunity in the New York Institute for the Education of the Blind to compare in a group of school children the tuberculin patch test with Mantoux tests done with 0.01 and 1.0 mg. Old Tuberculin; 177 subjects were tested in 1938 and 202 in 1940. There were 163 pupils who occurred in both series.

In reading the Mantoux test, we adhered to the standards of the National Tuberculosis Association, described by Aronson (19) as follows:

> "A reaction showing some redness and definite oedema more than 5 mm., and not exceeding 10 mm. in diameter, is recorded as a one-plus reaction. A two-plus reaction is an area of redness and oedema measuring from 10 to 20 mm. in diameter. A three-plus reaction is characterized by marked redness and oedema exceeding 20 mm. in diameter. A four-plus reaction consists of marked redness, oedema and an area of necrosis. A reaction with slight redness and a trace of oedema, measuring 5 mm. or less in diameter, is marked doubtful. If there is no oedema at the site of injection, even if a slight redness is present, the test is recorded as negative. In interpreting the tuberculin reaction it must be remembered that the redness has less significance than the oedema."

In reading the patch tuberculin test we followed the standards of the originator of the test, Dr. Hermann Vollmer (9), who was kind enough to read most of the tests with us. To avoid bias the readings were made in such a way that the result of the Mantoux test should not be known while the patch test was being examined.

The Mantoux tests were done with Old Tuberculin, furnished by the Department of Health of the City of New York.

The material for the patch tuberculin test was placed at our disposal by the Lederle Laboratories, Inc. In 1938, the patches were manufactured with regular Old Tuberculin of the Department of Health of the City of New York. In 1940, the patches were made with Old Tuberculin produced on synthetic media according to the Seibert method (20). Vollmer (3) states that the latter tuberculin is four times more potent than the type grown on beef broth, available in 1938.

The results from this series of observations are presented in table 2. The combined data for the two years show 31 negative patch tests in 114 Mantoux-positive children, that is, failure to identify infection in 27 per cent. Among 265 Mantoux-negative subjects there were 28 positive

patch tests, that is, an incidence of false positive reactions of 11 per cent. Since in both classes of unreliable tests the percentage of discrepancy is considerably higher than was observed by other investigators (table 1), these findings require additional comment.

With respect to failure of the patch test to identify infection demonstrable by the Mantoux test the results for the two years, 31 per cent in 1938 and 25 per cent in 1940, are consistent. Reference to table 1 shows that these figures are well above the 15 per cent, representing the combined experience of other authors, but below the individual experience of Peck who found such failure in 71 per cent. Wide divergencies of this type inevitably suggest that differences in technique in performing the test have influenced the results. We have done our best to avoid such

TABLE 2

Summary of the comparative value of Mantoux and patch tests done in the New York Institute for the Education of the Blind

YEAR	TOTAL NUMBER	BOTH TESTS NEGATIVE	BOTH TESTS POSITIVE	CONTROL POSITIVE, PATCH NEGATIVE	CONTROL NEGATIVE, PATCH POSITIVE	PER CENT FALSE NEGATIVE PATCH TEST	PER CENT FALSE POSITIVE PATCH TEST
1938	177	125	31	14	7	14/45 31%	7/132 5%
1940	202	112	52	17	21	17/69 25%	21/133 16%
1938 and 1940	379	237	83	31	28	31/114 27%	28/265 11%

Note: The control test consisted of 0.01 to 1.0 mg. Old Tuberculin intracutaneously.

errors but some have undoubtedly occurred. While the patches were on, the children refrained from physical activity in order to prevent excess perspiration. If, by accident, a patch came off prematurely, the test was repeated. In Peck's cases the existence of technical factors as causes of variability in response is indicated by his results when the patch test was repeated. Among 52 Mantoux-positive subjects who exhibited negative patch tests, repetition of the test yielded a positive result in 16 instances. Similarly in our series, among 30 cases where the patch test failed to identify infection, repetition of the test gave a positive result in 12 instances. We shall show presently that most of these difficulties arise in subjects in whom allergy to tuberculosis is low and where it is necessary to appraise the significance of borderline reactions. In reading

such tests it is almost impossible to avoid a personal bias, if the result of one test is known when the other is inspected. Some of the extremely low figures in the literature for failure of the patch test to identify infection may find their explanation in this circumstance.

The considerations outlined above lead to the conclusion that the patch test is capable of highly reliable results when performed under ideal conditions. Some of these conditions can be controlled by care in applying the test but unfortunately some, which depend on the cooperation of the subject, the season of the year and other factors influencing perspiration, cannot be controlled and will remain as causes of discrepant results.

The high incidence of false positive reactions shown in table 2 also demands comment. Here the figures for the two years, 5 per cent in 1938 and 16 per cent in 1940, are not consistent and indicate a statistically reliable increase in the incidence of such reactions. The reason for the increase is not entirely apparent. Subjective change in the attitude of the observer over the period of two years may have exercised some influence on the result. However, it should be noted that during the interim the tuberculin used in the patch test outfits was changed from material prepared on beef broth to material prepared on synthetic medium. Steward (14) also found that incidence of positive patch tests with negative Mantoux tests rose from 4 per cent to 8 per cent in a series of 48 subjects when tuberculin prepared on synthetic medium, instead of beef broth, was used.

Before commenting on the significance of these false positive reactions, it will be helpful to consider both types of unreliable patch tests from the standpoint of the degree of allergy exhibited by the subjects on whom the tests were performed. In our series there were 59 instances of contradiction between the two types of tuberculin tests. In 36 of these the induration of the Mantoux test was only 10 mm. or less in diameter and in 54 the patch test was recorded as only one-plus. Thus the majority of discordant results were obtained on subjects who exhibit slight or dubious reaction to tuberculin; the significance of false positive reactions must be viewed in this light. The criteria of the National Tuberculosis Association, used by us in reading the Mantoux test, represent the result of long and large experience. In drawing them up it was clearly recognized that no test for allergy can distinguish infallibly between infected and noninfected subjects, that it is wiser to overlook and set aside for further study, subjects in whom the presence of infection is dubious than

to brand as infected subjects in whom no infection is present. Undoubtedly, in its present form and with the present criteria for reading, the patch test will disclose the presence of tuberculous infection in cases where the Mantoux test has failed but it follows for the same reason that it will label as tuberculous a certain number of subjects in whom no infection is present.

In viewing both types of unreliable reactions collectively, it is clear that any attempt to decrease the incidence of false positive reactions by assuming a more conservative attitude in interpreting mild reactions must also increase the incidence of failure to identify the presence of infection. Undoubtedly a more rational method of interpretation can be reached. But it is clear that the period has not yet arrived when the time-proven Mantoux test can be replaced by an equally reliable contact test.

SUMMARY

The literature dealing with the tuberculin patch test has been reviewed in order to tabulate all instances in which the reaction was compared with an adequately performed Mantoux test. There is considerable variability among the findings of different authors. Therefore the pooled results might have to be changed at a later date when more and more homogeneous material will be at our disposal. The present combined data show that 15 per cent of Mantoux-positive subjects have exhibited a negative patch test, that 3 per cent of Mantoux-negative subjects have given a positive patch test.

Personal experience with comparative patch test and Mantoux test on 379 school children showed that 27 per cent of Mantoux-positive subjects exhibited a negative patch test while 11 per cent of Mantoux-negative subjects gave a positive patch test

The discrepancies in the results of different investigators are discussed in order to assist in assessing the reliability of the patch test.

CONCLUSION

The tuberculin patch test, because of simplicity of performance, has a limited field of usefulness. Evidence so far available does not indicate that it can be used to replace in reliability the well established Mantoux test.

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CLINICAL AND LABORATORY NOTES

TUBERCULOSIS IN IDENTICAL TWINS[1,2]

G. D. KETTELKAMP AND WILLIAM W. STANBRO

Chester and Chesley, white male, identical twins, aged seventeen, were admitted to Robert Koch Hospital on August 5, 1939, with a diagnosis of far advanced pulmonary tuberculosis. There was no hospital record of their birth, since they were delivered at home by a physician who is now dead. However, the mother states that she was told by the physician who attended her that "both babies were in the same sac and that there was only one afterbirth." Under like environment the course of development of the twins was similar. Chesley was a little larger than Chester but otherwise they looked very much alike. To the childhood diseases, which they had at the same time, their behavior was similar. The family history was negative for tuberculosis and there was no history of outside exposure to tuberculosis in either case.

Because of the remarkable similarity in the behavior of the twins to tuberculosis it was felt that the cases were of sufficient interest to report. In reviewing the literature it was found that this similarity in behavior of identical twins to pulmonary tuberculosis had been emphasized in several reports. Uehlinger and Künsch (1) reported tuberculosis in 46 pairs of twins, 12 of whom were identical and 34 of whom were fraternal. Their results were as follows:

In the 12 pairs of identical twins the behavior to tuberculosis was similar in 7 and dissimilar in 5; in the 34 pairs of fraternal twins the behavior to tuberculosis was similar in 2 and dissimilar in 32. These figures are even more striking when environment is considered. In the 12 pairs of identical twins environment was similar in 7 and dissimilar in 5; in the 34 pairs of fraternal twins, the environment was similar in 25 and dissimilar in 9.

Uehlinger and Künsch also gave, in their article, the results of Diehl and Verschuer which were as follows:

In 80 pairs of identical twins the behavior to tuberculosis was similar in 52 and dissimilar in 28; in 125 pairs of fraternal twins the behavior to tuberculosis was similar in 31 and dissimilar in 94.

Verschuer (2) reported 36 pairs of identical twins and 43 pairs of fraternal twins with tuberculosis in which the behavior was similar in 25 and dissimilar

[1] From the Robert Koch Hospital, Hospital Division, Department of Public Welfare, St. Louis, Missouri.

[2] Read before the St. Louis Trudeau Club, May 2, 1940.

in 11 of the identical twins, whereas in the fraternal twins the behavior was similar in 9 and dissimilar in 34.

Diehl (3) reported tuberculosis in 104 pairs of twins. In the 36 pairs of identical twins the behavior was similar in 25, or 69 per cent, and dissimilar in 11, or 31 per cent, whereas in the 68 pairs of fraternal twins the behavior was similar in 17, or 25 per cent, and dissimilar in 51, or 75 per cent.

Elizabeth Klein (4) reported tuberculosis in identical twins in which both died at ten and eleven months, respectively, and in which one of the pair developed a haematogenous spread with a resultant generalized miliary tuberculosis.

CASE REPORTS

CHESTER	CHESLEY
Clinical Histories	
Onset November, 1938 with a pain in the left side of the chest, cough and expectoration. Pulmonary tuberculosis was diagnosed in March, 1939. He was hospitalized in March, 1939. A left therapeutic pneumothorax was induced in June, 1939.	Onset in January, 1939 with pain in the left side of the chest, cough and expectoration. Pulmonary tuberculosis was diagnosed in April, 1939. A left therapeutic pneumothorax was begun in June, 1939.
Positive Findings on Admission to Robert Koch Hospital	
T: 101.7, P: 110, R: 26.	T: 100.2, P: 104, R: 24.
Height: 61 inches, Weight: 89½ lbs.	Height: 61¾ inches, Weight 101¼ lbs.
General appearance: poorly developed, emaciated and very weak.	General appearance: poorly developed, undernourished and weak, but somewhat stronger than Chester.
Eyes: left eye artificial as a result of an accident.	Eyes: negative.
Ears: negative.	Ears: chronic suppurative otitis media, left.
Chest: Left side: percussion note hyperresonant; tactile fremitus diminished; vocal resonance diminished; breath sounds suppressed; no râles.	Chest: Left side: percussion note hyperresonant; tactile fremitus diminished; vocal resonance diminished; breath sounds suppressed; few râles in apex.
Right side: negative.	Right side: negative.

Laboratory Findings

Urine: negative.
Sputum: positive for acid-fast bacilli.
Kahn: negative.
W.B.C.: 9,350.
Differential—39% segmented, 3% eosinophiles, 9% monocytes, 37% stabs, 12% lymphocytes.

R.B.C.: 3,250,000.
Hb.: 55%.

Urine: negative.
Sputum: positive for acid-fast bacilli.
Kahn: negative.
W.B.C.: 10,700.
Differential—43% segmented, 1% eosinophiles, 1% baseophils, 4% monocytes, 27% stabs, 24% lymphocytes.
R.B.C.: 3,900,000.
Hb.: 72%.

Roentgenological Examination

Left pneumothorax in which there was a fairly good collapse. There was a small amount of fluid in the left base. The markings in the right lung were rather heavy.

Pneumothorax on the left in which there was a moderate collapse. There were several long adhesions to the apex. There was a moderately heavy infiltration throughout the middle third of the right lung.

Hospital Course

The left pneumothorax was continued with weekly refills of 400 to 600 cc. of air, beginning and ending with negative pressures. The mediastinum was very labile. He did poorly, going down-hill progressively, with daily elevations in temperature and a steady decline in weight. He developed hoarseness and pain in his throat on swallowing. He suffered with bouts of diarrhoea and abdominal cramps. On December 9, 1939, about five days after his last pneumothorax refill, he developed a left spontaneous pneumothorax. Air was removed on five occasions in the next three days for relief of dyspnoea

The left pneumothorax was continued with weekly refills of 400 to 600 cc. of air, beginning and ending with negative pressures. The mediastinum was very labile. He did poorly, going progressively down-hill with daily elevations in temperature and a steady decline in weight. He became hoarse. He developed an obstinate diarrhoea, frequently accompanied by severe abdominal cramps. On October 4, 1939, several days after his last pneumothorax refill, he developed a left spontaneous pneumothorax. Air was removed from the left chest on two occasions for relief of dyspnoea. He developed fluid on

and thereafter air was removed once a week. On March 5, 1940, the air removed from his left chest had a very foul odor. He died on the evening of March 5, 1940, the disease having progressed with no remissions from date of admission.

the left which, with discontinuation of the left pneumothorax and re-expansion of the lung, was absorbed. He died on February 11, 1940, there having been no remissions in the progress of his disease.

Autopsy Findings

1. The left pleural cavity was filled with thin foul-smelling pus.
2. The laryngx showed marked oedema of the epiglottis and arytenoids with extensive ulceration extending downward to involve both the false and true cords. Microscopical examination revealed numerous tubercles, only a few of which contained giant cells.
3. The trachea showed extensive ulceration with numerous tubercles on microscopical examination.
4. The left lung was collapsed to one-half its usual size and a bronchopleural fistula was present. Numerous large caseous tubercles, none of which were encased in a fibrous capsule, and only a few of which contained giant cells, were present. There were several small cavities. Numerous caseous tubercles and several thin-walled cavities were present in the right lung.
5. Microscopical examination of the liver and spleen revealed several tubercles.
6. Beginning in the lower part of the

1. The right pleural cavity contained 300 cc. of a cloudy straw-colored fluid.
2. The larynx showed a small circumscribed ulcer about 0.5 cm. in diameter on the right true cord.
3. In the left main bronchus, about 1 cm. distal to the carina, there was a roughening of the mucosa which on microscopical examination showed several non-giant cell-containing tubercles.
4. On the surface of the right lung were numerous caseous tubercles. There was no portion of the right lung which was not involved either in the form of tubercles or cavities. The left lung showed several cavities in the upper lobe and caseous tubercles scattered throughout the remainder of the lung. No giant cells were found in these tubercles and no fibrous tissue capsules surrounded them.
5. The liver and spleen showed microscopical tubercles.
6. Beginning in the first part of the

jejunum and extending distally to involve the remaining small bowel and the entire large bowel, were numerous ulcerations which microscopically revealed tubercles of the giant cell and non-giant cell-containing varieties.	jejunum and extending throughout the remainder of the small bowel and all of the large bowel were numerous ulcerations.
7. Microscopical examination of appendix showed several tubercles.	7. Microscopical examination of the appendix revealed a small non-giant cell-containing tubercle.
8. No tuberculosis of kidneys found.	8. In the cortex of the right kidney there was a small yellow nodule which on microscopical section was found to consist of several tiny conglomerate tubercles.

DISCUSSION

It is felt that the similarity of behavior in this instance of tuberculosis in identical twins is the result of identical inheritance. This conclusion is borne out by the results given in the discussion of the literature. Although in this particular instance the environment was similar, Uehlinger and Künsch point out that in spite of the fact that in their series the fraternal twins had similar environment in 73 per cent of the cases, only 5 per cent were similar in their behavior to tuberculosis, while identical twins had similar environment in only 58 per cent of the cases and still 58 per cent were similar in their behavior to tuberculosis. Another point of interest in these cases is the likeness of the tissue response to the tuberculous infection. In both twins there was a paucity of giant cells and no evidence of fibrous tissue capsules about tubercles.

SUMMARY

Chester and Chesley, seventeen years old, identical twins, entered Koch Hospital on August 5, 1939 with a history of common initial symptoms of pain in the left chest, cough and expectoration. A therapeutic left pneumothorax had been started on them both in June, 1939. The clinical course was similar, both going progressively down-hill, both developing symptoms of laryngeal and intestinal tuberculosis and both developing left spontaneous pneumothorax several days after their last refill. Postmortem examination revealed each to have tuberculosis of the lung, larynx, intestines, liver and spleen. In both there was a paucity of giant cells and no evidence of fibrous capsules about tubercles.

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EYE COLOR AND TUBERCULOSIS[1, 2]

EMIL BOGEN

The phthisic diathesis of Hipprocrates, as well as the quite contrary scrofulous diathesis of Hufeland, agree in characterizing the form of the body peculiarly subject to this complaint as possessing blue eyes (1). Although this concept has been less emphasized in recent years, its persistence in text-books and other literature seemed to justify an attempt at its quantitative verification.

The color of the eyes has been recorded for all patients admitted to the Olive View Sanatorium during the past two decades. For the purpose of this study, all of the darker colored eyes, described as black, brown, dark brown, light brown or gray brown, have been considered together as contrasted with the lighter group of blue, light or dark blue, blue gray, gray, hazel or green eyes.

We do not have any information as to the actual frequency of distribution of the different eye colors in the entire community, and so the fact that more dark-eyed individuals were admitted together than light-eyed individuals, may not be interpreted to mean that dark-eyed persons are more apt to develop the disease.

The stage of disease, at the time of admission, in patients with the different colored eyes was, in general, quite similar, about two-thirds of both groups being far-advanced at the time of admission. Slightly less dark-eyed individuals were admitted in the minimal stage, however. This may reflect the fact that dark eyes are more common in the Mexicans and Negroes who are less frequently diagnosed early, perhaps chiefly because of cultural and environmental factors (2).

The course of the disease, after admission to the Sanatorium, however, is less affected by these previous environmental differences. Here, it is found that there has been practically no difference. The case fatality rate among patients in the three different stages of the disease, cared for at the Olive View Sanatorium, has been practically the same in patients with light and dark pigmented eyes (3). Differences in individual susceptibility to tuberculous infection may exist in different groups, but it does not appear likely that any

[1] From Olive View Sanatorium, Olive View, California.

[2] With the aid of Work Projects Administration, Project No. 665-07-3-223, Los Angeles County, California.

such differences are associated with differences in the pigmentation on the iris of the eye.

Eye Color and Tuberculosis

	DARK EYES				LIGHT EYES			
	Patients	Died	Years followed	Per cent	Patients	Died	Years followed	Per cent
Minimal	403	24	1,980	1.2	368	30	2,204	1.3
Moderate	674	92	2,324	4.0	421	85	1,676	5.0
Far advanced	3,203	1,776	7,994	22.2	2,438	1,382	6,648	20.8
Childhood and nonpulmonary	605	41	2,588	1.6	333	27	1,512	1.7
Total	4,885	1,933	14,886	13.0	3,560	1,524	12,040	12.7

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FIBRIN-BODIES IN PNEUMOTHORAX[1]

W. H. OATWAY, JR.

Fibrin-bodies are considered to be concretions of fibrin which occur in the presence of fluid. They may form free or attached to adhesions. They may remain for long periods, may degenerate, may organize (if attached to a blood supply) or may disappear. They may also have peculiar complications.

Fibrin-bodies have not uncommonly been described in cases of intrapleural pneumothorax. Recent articles on extrapleural pneumothorax have contained occasional references to the possibility of fibrin-body formation, and one author has noted this occurrence in his series.

Two instances of fibrin-body formation in extrapleural pneumothorax are reported here. Each developed in the presence of fluid. One occurred shortly after operation, the other six months later. Both were apparently unattached. One was solid, but slowly liquefied after the induction of oleothorax, and the other became inflated during the aspiration and replacement of fluid with air.

Case 1: A white male, aged thirty-nine. The original lesion was chronic, bilateral, apical with moth-eaten cavitation. A healed Pott's disease of twenty years' duration had left an S-shaped kyphoscoliosis. Intrapleural pneumothorax was impossible on either side. An extrapleural pneumothorax was induced in the upper third on the right side, and considerable serosanguineous fluid formed after operation. This was aspirated with some difficulty due to the kyphosis. At the end of a week it was obvious that an amorphous body was present in the residual fluid, and this gradually assumed an oval shape with no mural connection. (See films of case 1, (a) and (b).)

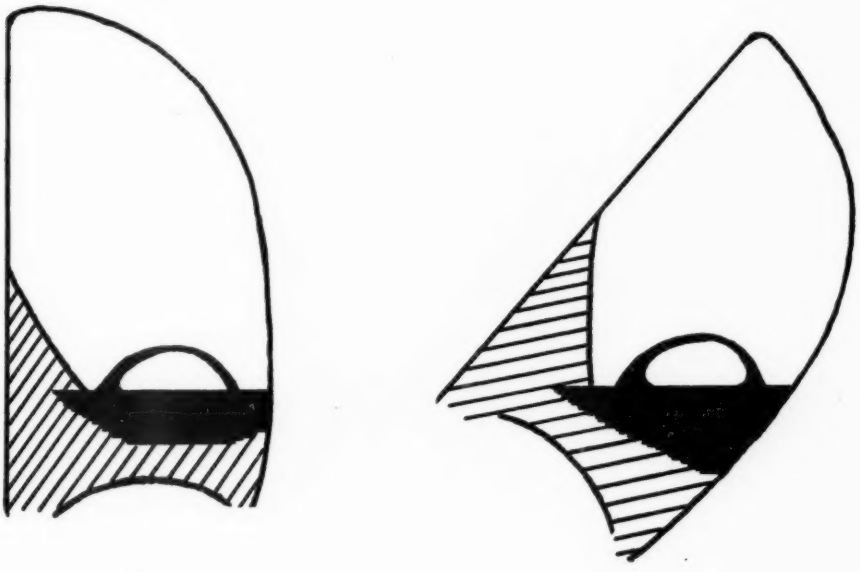
Five months after the operation the pneumothorax was unchanged, the fibrin-body was slightly smaller, and a small amount of thick, sterile, tan-colored fluid was present. The pneumothorax was converted to oleothorax without incident. A few cc. of fluid have been aspirated at intervals since (although the oil pressures have not risen), and the fibrin-body disappeared. It is probable that the free fibrin-body slowly liquefied.

Case 2: A white female, aged twenty-eight. The original lesion was unilateral and caseo-pneumonic. Intrapleural pneumothorax was inefficient because of

[1] From the Thoracic Service, State of Wisconsin General Hospital, and Medical School, University of Wisconsin, Madison, Wisconsin.

a b

FIG. 1. Case 1. (a) Left: Patient tilted to his right. (b) Right: Patient tilted to his left; fibrin-body moves freely.



a b

FIG. 2. Case 2. Floating, inflated fibrin-body. (a) Left: Patient erect. (b) Right: Patient tilted to her left.

adhesions, and later the lung could not be reëxpanded. A phrenic crush was of no help. The bronchi were clear.

A large extrapleural pneumothorax was then done, with a good collapse of the lung The course was uneventful for six months, when a clear fluid began to form. After weekly aspirations, the formation decreased and oleothorax was attempted. Because of continued effusion the oil was removed. A few weeks later a fibrin-body was noted, about 4 x 7 cm. in size, unattached and floating in the fluid. This came down against the tip of the needle at the end of each aspiration. After several weeks and at the conclusion of an aspiration with replacement of the fluid by air, fluoroscopy showed a peculiar phenomenon which was confirmed by X-ray films. The fibrin-body had become inflated during the aspiration procedure. (See X-ray drawings of case 2.) A month later, and over a period of two weeks, the fibrin-body disappeared, with no change in the clear quality of the fluid.

TRAY FOR STAINING TUBERCLE BACILLI[1]

WILLIAM STEENKEN, JR.

One of the most frequent criticisms of the staining for tubercle bacilli of many slides in the same jar at the same time, is that negative smears may become contaminated with acid-fast organisms from highly positive smears.

To answer this criticism a tray has been designed to stain at one time 6 slides, smeared with sputum or other tuberculous material. It may be used for rapid, or overnight staining of such preparations.

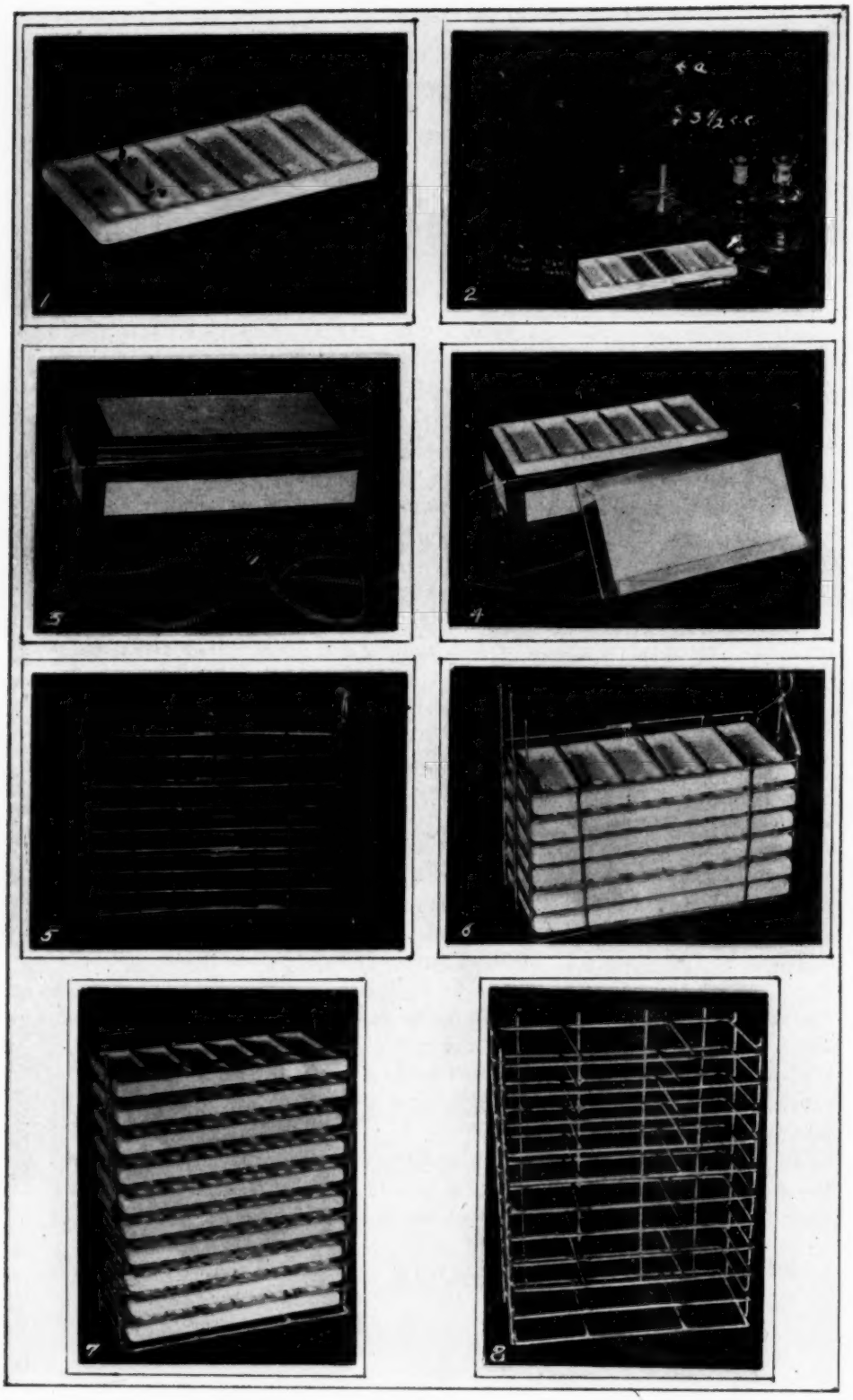
Rapid method: If the tray is used for rapid staining, carbol fuchsin is added, with the aid of a pipette or burette (figure 2-a), to each small compartment (figure 1-a) until the small elevations (figure 1-b) are covered with the dye. (The height of the elevations is fixed so that the amount of stain required to cover them—3.5 cc.—will be approximately the same as that used for flooding a slide.) The smears are then fixed by heating and placed, *smear side down*, in each compartment of the staining tray. The tray is now placed in a small electric oven (figures 3 and 4) and heated at 50°C. for approximately fifteen minutes and is then taken out of the oven and allowed to cool. Each slide is removed from the tray and decolorized separately, first with acid alcohol, then alcohol, and finally counterstained with brilliant green, or methylene-blue, as one may prefer.

Overnight method: The overnight method is especially helpful when large numbers of specimens are to be examined. It allows one day for the preparation and smearing of the specimens, and the next day for decolorizing, counterstaining and microscopical examination.

The slides are prepared in the same manner as for rapid staining and placed in the trays containing the dye. The trays are then placed in wire racks (figures 5, 6, 7 and 8), and set in a humidor in the incubator at 37.5°C. overnight. The following morning the wire rack containing the trays is removed, and the trays cooled at room or icebox temperature. The slides are then removed from the compartments and washed, decolorized and counterstained separately as previously mentioned.

The stain employed in these trays is prepared according to Cooper (1) with the exception that in this laboratory 0.5 cc. instead of 3.0 cc. of 10 per cent sodium chloride per 100 cc. of Ziehl-Neelsen carbol fuchsin is used.

[1] From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.



FIGS. 1–8

DISCUSSION

The criticism that acid-fast organisms may be transferred from slide to slide is a just one, but experimental data are lacking to prove that acid-fast organisms from highly positive slides may contaminate negative smears when stained in the same jar and in the same solution at one time.

Often smears that are reported as negative by the regular routine examination—twenty minutes—are found to be positive after prolonged microscopical inspection, and conversely, smears that contain a few acid-fast organisms, as revealed by the routine examination, may be considered as negative after repeated inspection by another examiner. It is, therefore, difficult to prove whether or not contamination with acid-fast organisms has taken place.

However, to guard against the possibility of contamination we have adopted this multiple staining technique, whereby each slide is stained individually in the same unit at the same time.

The tray and small heating oven described for this purpose is well suited for use in small laboratories that do not have gas.

The trays are made of glazed porcelain so that they can and should be burned out with cleaning solution (sulphuric acid and potassium dichromate) between each use in order to prevent any possible carrying over of acid-fast organisms from one slide to another.

The complete staining equipment may be obtained from The Will Corporation, Rochester, New York.

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Fig. 1. Porcelain staining tray.
Fig. 2. Burette used for adding stain to small compartments of tray.
Fig. 3. Heating oven closed.
Fig. 4. Heating oven containing staining tray.
Fig. 5. Small wire rack.
Fig. 6. Small wire rack containing staining trays.
Fig. 7. Large wire rack containing staining trays.
Fig. 8. Large wire rack.

COMMUNITY SURVEY FOR TUBERCULOSIS[1]

ROBERTS DAVIES AND CHARLES S. ROBB

For many years tuberculosis workers have hoped for eventual eradication of the disease. Yet, despite declining death rates, eradication appears unlikely with present methods of control. Pessimism regarding the ultimate effectiveness of examination of contacts and segregation and treatment of active cases seems to be well founded. The fact that few, if any, communities have actually been able to examine adequately and repeatedly all contacts of open cases and to segregate all active cases throughout the period of activity indicates a practical if not a theoretical defect in the method.

Patients with active disease often give no history of exposure to tuberculosis and frequently examination of all their intimate contacts fails to reveal a source of infection (1). In some cases, more or less casual contact may be of more significance than is ordinarily assumed. In others, especially in older age groups, the disease may represent reactivation of a latent lesion many years after the original contact was broken. At any rate such cases show that the most thorough contact-examination program cannot hope to find all the active cases of tuberculosis in a community, much less find them in an early stage of their disease.

Partly because of the recognized deficiencies in our present programs, there has been a growing interest in mass surveys designed to find all the tuberculosis in a given group. Surveys of schools, factories and various public institutions have been reported with increasing frequency.

In 1937, Nopeming Sanatorium and the St. Louis County Health Department made a tuberculin and X-ray survey of the entire population of a rural township (1). Six new cases of tuberculosis were found in a community of 367 persons. Since that time several reports of similar complete community surveys have appeared (3, 4, 9) and the importance of mass surveys of special population groups has been emphasized (5, 6, 7, 9, 10). An especially valuable contribution is the report of H. R. Edwards on the surveys made by the New York City Department of Health (2).

In the summer of 1939, Nopeming Sanatorium made another survey of three more townships in St. Louis County. Our method was the same as that used in our previous survey. We visited each house in the community, explained the purpose of the survey, took a brief history of the family, and gave tuber-

[1] From Nopeming Sanatorium, Nopeming, Minnesota.

culin tests to everybody. The first skin test was given with the usual first-strength dose of .000,02 mg. of PPD. Reactions were read in forty-eight hours and all negative reactors were given a second test of .002,5 mg. of PPD, or one-half the usual second-strength dose. Positive reactors were brought to the Sanatorium for X-raying. Single 14″ by 17″ chest plates were taken at 72″ with 0.1 second exposure, using 100 milliamperes and from 66 to 90 kilovolts. All films were read either by Dr. G. A. Hedberg of the Sanatorium staff or by the senior author.

The total population of the communities studied is 1,215. Approximately 77 per cent of the population is Finnish; 12 per cent, Scandinavian; and 11 per cent belong to other nationalities. About 35 per cent of the population is foreign-born. Most of the people make a living on their farms. The soil is relatively unproductive and the people are poor.

Of the 1,215 people in the three communities, 116, or 9.5 per cent, were not adequately examined. Some of these had negative first-strength tuberculin tests but no repeat skin test or X-ray examination; some had positive tuberculin tests but no X-ray film; and a few were not examined at all. Sixty-two, or 5 per cent, refused examination.

The distribution of positive reactors by age, sex and nationality revealed nothing of particular interest. Fifty-five per cent of the males and 46 per cent of the females had positive tuberculin reactions. Forty-one per cent of the reactors were positive only to the second test. Fifty-three per cent of the Finnish people and 47 per cent each of the Scandinavian and the group of "other nationalities" had positive skin tests. These percentages are corrected for age distribution. There is no mathematical assurance that the slight differences observed between nationalities could not be due to chance.

Of the 572 persons X-rayed, 349 were negative; 46 had evidence of pleurisy only; 75 showed evidence of primary infection; and 52 showed secondary or adult-type tuberculosis. Only one case had a lesion that appeared active. This man was immediately hospitalized and treated. All cases showing secondary lesions were filed for repeat films.

The great difference in the number of new cases of active tuberculosis found in our two surveys (6 from a population of 367 compared to 1 from a population of 1,215) probably reflects a real difference in the tuberculosis status of the communities involved, since there is a similar difference in percentage of positive skin tests and of apparently inactive adult-type lesions. The comparable percentages after correction for differences in age distribution are: first survey —positive reactors 59 per cent, inactive lesions 15 per cent; second survey—positive reactors 52 per cent, inactive lesions 7 per cent. Only 3 times in 100 could such a difference in positive skin tests be due to chance and only once in 500 times would such a difference in the incidence of inactive lesions occur by chance.

These differences in the two communities possibly reflect the differences in percentage of foreign-born persons. In the first survey, 65 per cent were foreign-born and in the second survey only 35 per cent. In comparable age groups 86 per cent of foreign-born persons had positive skin tests as compared with 64 per cent of those of native birth. Age, nationality, sex and economic status do not seem to be significant factors in explaining the differences between the two communities, since correction was made for variation in age distribution, the three nationality groups showed no significant differences in percentage of positive reactors or X-ray lesions, and sex distribution and economic status did not vary significantly between the two survey groups.

Complete community surveys such as these are expensive and for that reason inefficient, except where the incidence of clinically important tuberculosis is unusually high. However, the recent development of fluorographic methods, by greatly reducing the cost of X-ray examination and eliminating the need for tuberculin screening, may make much more extensive application of the method practical (8).

If such a complete community survey could be conducted annually, most cases of tuberculosis would be discovered and segregated relatively early. Morbidity should drop considerably within a few years and it would seem reasonable to hope that within perhaps thirty years tuberculosis would be a negligible problem. The cost would no doubt be considerably less than the enormous sums spent to control typhoid fever by insuring uncontaminated water supplies.

SUMMARY

1. The results of a complete community survey for tuberculosis are presented.

2. In the future, use of fluorographic methods may make such surveys cheaper and therefore more practical.

3. The possibility of eventual eradication of tuberculosis by more extensive use of the community survey is suggested.

We wish to thank Dr. C. A. Scherer, St. Louis County Health Officer, and his staff for coöperation and assistance, and the St. Louis County Tuberculosis and Public Health Association for the financial aid which made this survey possible. We are grateful to Dr. H. E. Hilleboe, Medical Coördinator of the Minnesota State Department of Social Security, for assistance in tabulation and analysis of statistical data.

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PULMONARY INSUFFICIENCY[1,2]

II. The Effects of Various Types of Collapse Therapy upon Cardiopulmonary Function[3]

ANDRE COURNAND AND DICKINSON W. RICHARDS, JR.

The clinical tests described in the preceding paper (1) have been used in an attempt to estimate the effect of various methods of collapse therapy upon pulmonary and circulatory function. The present report is based upon the study of 45 cases of chronic pulmonary tuberculosis.

MATERIAL

The mode of grouping, physical characteristics and clinical features of these 45 cases are presented in tabular form (tables 1 and 2).

Thirty-one cases have been studied before and after thoracoplasty. These may be subdivided into 5 groups in the following manner:

First Group: Thirteen cases without artificial pneumothorax or phrenic paralysis at the time of thoracoplasty. This group is not very homogeneous with regard to extent of lesions. In 9 out of 13 cases, the indications for thoracoplasty were ideal, according to our present standards. The 4 remaining cases were decidedly second choice on account of the extent of lesions; one of these cases had a discrete bilateral silicosis, with moderate pulmonary emphysema. The diaphragmatic motion was practically negligible in this case, in contrast to the rest of the group, in which a large diaphragmatic excursion on both sides was maintained.

Second Group: Five cases of artificial pneumothorax, complicated with tuberculous empyema, in which thoracoplasty was performed in order to obliterate the pleural space, with or without the additional indication of collapsing an apical cavity. The average duration of disease here was much greater than in the previous group.

Third Group: Three cases with partial and ineffective artificial pneumothorax. In these, following a limited upper thoracoplasty, the

[1] From the Tuberculosis Service, First Division, Bellevue Hospital, and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York City.

[2] Under a grant from the Commonwealth Fund.

[3] Presented in part at a session of the Clinical Section at the 35th annual meeting of the National Tuberculosis Association, Boston, Massachusetts, June 28, 1939.

remaining lung was then completely or partially reëxpanded. The average duration of disease was the shortest of all the groups studied.

Fourth Group: Five cases with permanent diaphragmatic paralysis on the side on which thoracoplasty was to be performed. In only 2 out of 5 cases was the extent of the unilateral lesion strictly limited to an apical cavity. The average duration of disease here was the longest of any of the groups.

TABLE 1

Physical characteristics in seven groups of patients studied

GROUP	NUMBER OF CASES	SEX	AGE (YRS.)			STATURE (CM.)			BODY SURFACE AREA (SQ.M.)		
			Mean	Standard deviation	Variation	Mean	Standard deviation	Variation	Mean	Standard deviation	Variation
I	13	5 M 8 F	33.4	8.4	19–45	171.3	12.4	159–191	1.74 (1.71)	.20 (.21)	1.41–2.14 (1.38–2.14)
II	5	3 M 2 F	27.4	7.3	22–40	166.3	14.7	148–180	1.71 (1.68)	.26 (.19)	1.38–2.04 (1.55–2.01)
III	3	1 M 2 F	28.0	—	21–35	166.0	—	161–170	1.70 (1.77)	— —	1.54–1.86 (1.58–1.97)
IV	5	2 M 3 F	34.4	12.3	21–52	163.3	8.9	157–171	1.69 (1.65)	.18 (.17)	1.43–1.90 (1.39–1.85)
V	5	2 M 3 F	37.6	10.6	24–49	163.4	5.2	159–170	1.64 (1.59)	.18 (.18)	1.51–1.92 (1.41–1.85)
VI	3	2 M 1 F	27.3	—	25–31	171.3	—	163–175	1.83	—	1.60–1.98
VII	11	3 M 8 F	32.1	6.6	20–40	165.5	8.0	158–180	1.76	.21	1.51–2.11

In brackets, body surface area in sq.m. following thoracoplasty.

Fifth Group: Five cases of fibrothorax with a large excavation in the upper half of the chest. This group was considered separately from the first, because of the marked contraction of the chest on one side, with a high, more or less immobile diaphragm, apparent emphysematous distention of the opposite lung, displacement and torsion of the heart with possible resulting obstruction of blood circulation in the various mediastinal vessels. In one case fibrothorax was apparently the result of

TABLE 2

Clinical features and mode of groupment of 45 cases studied

GROUP	DIFFERENTIAL CHARACTERISTICS OF GROUP	CLINICAL DURATION OF DISEASE (MONTHS)		RIBS RESECTED, NUMBER		SIDE	INTERVAL BETWEEN LAST STAGE AND FINAL STUDY (MONTHS)		MAXIMUM DIAPHRAGMATIC EXCURSION (CM.)			
									Right		Left	
		Mean	Variation	Mean	Variation		Mean	Variation	Mean	Variation	Mean	Variation
I	No artificial pneumothorax. No phrenic paralysis when thoracoplasty performed	38.2	3–192	7.1	3–9	Rt—8 Lt—5	5.0	3–11	3.5 (3.3)	0.5–6.5 (0.5–7.5)	4.1 (3.7)	0.5–7.5 (0.5–7.5)
II	Artificial pneumothorax complicated with empyema before thoracoplasty	64.8	24–180	7.0	5–9	Rt—2 Lt—3	4.8	3–9	2.6 (2.8)	2.0–6.0 (0 –6.0)	2.5 (1.6)	0.5–8.0 (0 –6.0)
III	Artificial pneumothorax reëxpanded after thoracoplasty	10.3	6–18	5.7	5–6	Rt—2 Lt—1	10.3	7–13	2.7 (4.7)	0–7 (3–7)	2.8 (2.8)	0–5 (0–5)
IV	Phrenic interruption before thoracoplasty	66.0	15–132	6.8	3–10	Rt—4 Lt—1	10.0	3–24	1.7 (1.7)	0–7 (0–7)	3.6 (3.5)	0 –7.5 (0 –7.0)
V	Fibrothorax with immobile diaphragm before thoracoplasty	52.2	6–120	9.8	9–11	Rt—1 Lt—4	4.4	3–6	4.0 (3.8)	0–8 (0.5–8)	1.2 (1.3)	0 –6.0 (0 –6.0)
VI	Phrenic interruption; thoracoplasty not completed	24.0	13–36	None		Rt—3			0.3	0 –0.5	3.2	2.5–4.5
VII	Reëxpanded pneumothorax	42.6*	24–60	None		Rt—5 Lt—7‡	41.5†	10–72	3.8	2–6	4.0	0.5–8.5

In brackets, maximum diaphragmatic excursion in cm. following thoracoplasty.

* Duration of artificial pneumothorax.

† Interval between reëxpansion and study.

‡ One case of bilateral artificial pneumothorax.

pleurisy following the reëxpansion of an ineffective artificial pneumothorax. In 3 cases there was a clinical history of endobronchial lesion which was confirmed in 2 cases by bronchoscopy. The average duration of disease was, as one would expect, greater than in the first group.

The remaining 14 cases of chronic pulmonary tuberculosis were studied after completion of other forms of collapse therapy, but were not studied before collapse.

Sixth Group: Three cases with diaphragmatic paralysis following phrenic crushing. Thoracoplasty was attempted in all 3, but not completed for reasons to be discussed later. By adding to these 3 cases, the 5 cases of group IV studied before thoracoplasty, the state of pulmonary and circulatory function in a total of 8 cases of therapeutic phrenic paralysis could be assessed.

Seventh Group: Eleven cases after reëxpansion of artificial pneumothorax. In comparing this group with the others, it must be noted that all these subjects had resumed normal activity, the average interval of time since reëxpansion being 41.5 months.

METHODS

The methods used in this study have been described in the first paper of this series (1). In addition, the total lung volume and its subdivisions were determined. Measurement of the residual air volume was made according to the "closed circuit" method described by Christie and modified by us (2). This method, as we recently pointed out, gives at times erroneously large values, especially when pulmonary emphysema is present (3). A new method of determination of residual lung volume (4) was not available before completion of this series. In predicting the normal absolute and relative values of lung volumes, we used regression formulae calculated by Kaltreider, based upon age, sex and height (5).

PROCEDURE

The course of procedure was as follows: Patients to be investigated were made familiar with the methods to be used before actual determinations were carried out. On the first morning, a sample of arterial blood was obtained under basal conditions. Then ventilation at rest, during exercise and during recovery was measured and samples collected; the second arterial puncture being performed not later than the end of the first minute of recovery following exercise. In the afternoon, the infusion test was performed, and the next morning lung volumes and maximum breathing capacity in the recumbent and standing positions were measured. All determinations of the state of the respiratory gases in the expired air and in the blood were done in duplicate.

In the cases studied prior to thoracoplasty, the patients were ambulatory, as a preparatory procedure to surgical intervention. Studies following thoracoplasty were made at a time when the patient had been allowed to resume activity.

RESULTS

The data for the 7 groups are presented in tables 4 to 11 (at the end of the paper). Means, standard deviations, and in a few instances the range of variation, are tabulated. The mean values for each measurement in each group are also assembled in chart form (charts 1, 4, 7, 9, 11 and 12).

A. *Effect of Thoracoplasty upon Pulmonary and Circulatory Function Group without Artificial Pneumothorax or Phrenic Paralysis—Group I (Chart 1)*

In this group of 13 cases of chronic pulmonary tuberculosis, the influence of the disease itself upon pulmonary function prior to thoracoplasty is shown.

(a) *Preoperative state:* The average total capacity was 80.3 per cent of the predicted value. This was due to a large decrease in the absolute value of vital capacity which was 62.9 per cent of the predicted value. The residual air volume was slightly greater than the predicted value. Thus the ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ was greater than normal. Maximum breathing capacity was greatly reduced, to 53.7 liters per minute, corresponding to 45 per cent of the average maximum breathing capacity in a group of normal subjects with the same sex distribution.[4] Ventilation per minute at rest was significantly larger than in the control group (P between .05 and .02). As a result, the breathing reserve at rest was only 86.8 per cent of the maximum breathing capacity. (In normal subjects, it is always above 92 per cent.) Ventilation during the performance of standard exercise showed no significant difference from control values. The rates of oxygen intake and of carbon dioxide elimination were significantly lower ($P = .01$ for both) than in the control group. But both

[4] To obtain this percentage value, it is assumed that, in a group of normal subjects composed of 5 males and 8 females, each male's maximum breathing capacity would equal 154 liters and each female's maximum breathing capacity would equal 100 liters, both these values representing the average found in normal subjects. These percentage values are given here only as approximations (see part I of this paper).

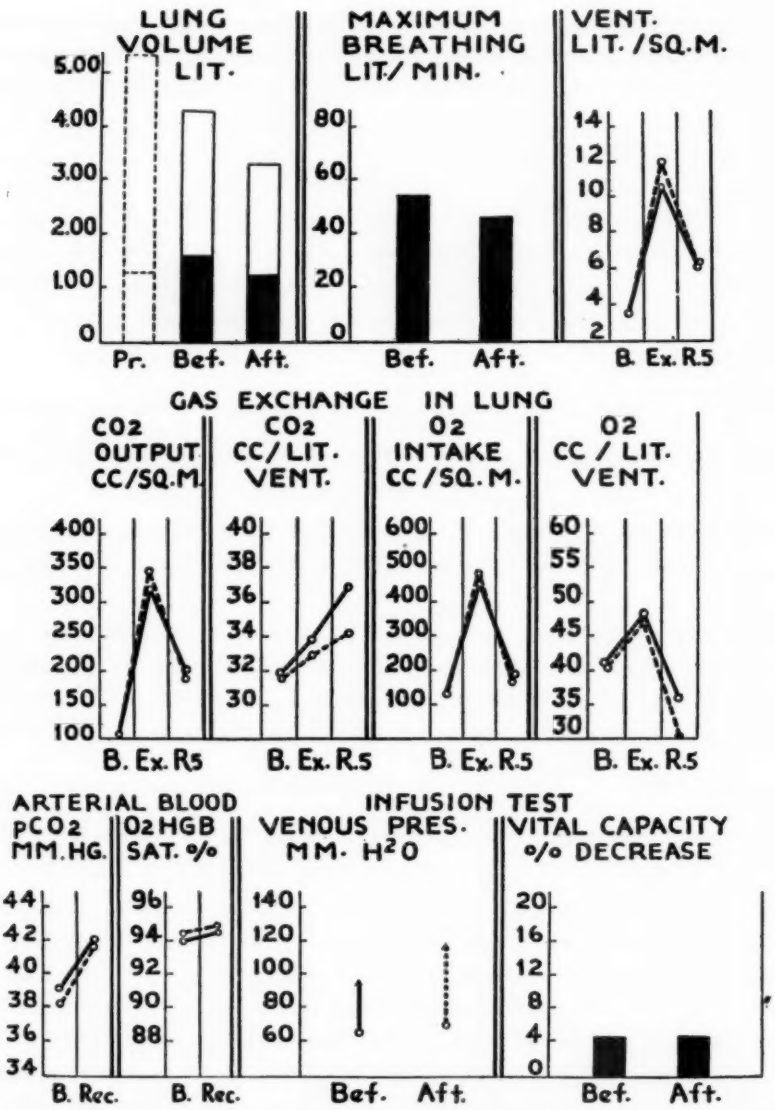

CHART 1. Mean values of principal measurements in 13 patients of group I, before and after thoracoplasty.

Lung Volume, liters. "Bef." = values before thoracoplasty; solid block = residual air volume; white block = vital capacity (complemental plus tidal plus reserve air); total height of block = total lung volume. "Aft." = similar values after thoracoplasty. "Pr." = similar values, for normal individuals of same size, sex and age distribution as patients in group I.

Maximum Breathing, liters per minute. "Bef." = mean maximum breathing capacity before thoracoplasty; "Aft." = after thoracoplasty.

these measurements increased appreciably during the performance of standard exercise. In the arterial blood, oxyhaemoglobin saturation per cent was 94.0 at rest and 94.5 during early recovery from exercise. In 2 cases only were the values lower than the accepted lower level of normal. During early recovery, there was a slight persistent increase in carbon dioxide tension and a decrease in pH from 7.43 to 7.36, which was to be expected in a group of patients whose state of physical training was decidedly poor. The state of the circulation, as revealed by the variations in venous pressure, circulation time and vital capacity in relation to the infusion test, appeared to be essentially normal in this group. In no case did the vital capacity decrease by more than 7 per cent, following infusion.

Decrease in vital capacity, relatively large residual air probably due to a mild degree of emphysema, moderate degree of ventilatory insufficiency and decreased efficiency of ventilation (lower percentage removal of oxygen from inspired air at rest) were thus the main preoperative findings. There was no other evidence of respiratory insufficiency nor any manifestation of cardiocirculatory insufficiency.

(b) *Postoperative state:* Following the resection of an average of 7.1 ribs, there was evidently a significant decrease in the absolute volumes of total capacity and residual air (P .01), and a less significant decrease in vital capacity (P between .05 and .02). In percentage of preoperative values, the total capacity decreased by 25 per cent, the vital capacity by

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Vent., lit./sq.m. = pulmonary ventilation in liters per square meter of body surface. "B." = basal (resting) conditions; "Ex." = during standard exercise; "R.5" = during fifth minute of recovery following exercise. Solid line = before thoracoplasty; dotted line = after thoracoplasty.

Gas Exchange in Lungs. CO_2 output in cc. per square meter of body surface; other symbols are the same as for Ventilation above. The remaining three graphs under Gas Exchange in Lung describe in similar terms: CO_2 output expressed as cc. per liter of ventilation; O_2 intake in cc. per square meter of body surface; and O_2 intake in cc. per liter of ventilation.

Arterial Blood. pCO_2 mm. Hg. = CO_2 pressure in mm. mercury, in the arterial blood, under conditions of rest (B) and recovery (Rec.) one minute after exercise. Solid line = before thoracoplasty; dotted line = after thoracoplasty. O_2 Hgb. sat. % = arterial oxygen saturation per cent, under similar conditions.

Infusion Test. Venous pres., mm. H_2O = venous pressure in mm. of water. Circle = value at rest, arrow point = value at end of 1,500 cc. intravenous infusion. Solid line = before thoracoplasty; dotted line = after thoracoplasty. Last graph describes the *per cent decrease* in vital capacity occurring after the 1,500 cc. infusion; "Bef." = before thoracoplasty, "Aft." = after.

24.7 per cent, but the ratio of $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ remained practically unchanged. Maximum breathing capacity decreased by 16 per cent. With an unchanged ventilation at rest, the breathing reserve,[5] at 84.4 per cent of the maximum breathing capacity, had decreased by 2.4 per cent. The only added change from the preoperative state was an increase in ventilation during exercise, a change hardly significant (P between .1 and .05). Otherwise all the measurements of gas exchange in the lungs, state of respiratory gases in the arterial blood and state of the circulation were exactly what they were before.

A large change in total lung volumes, a small decrease in maximum breathing capacity and an increase in ventilation during exercise, thus constituted the only further detrimental effects upon pulmonary function due to thoracoplasty. The cumulative effect of reduced maximum breathing capacity and increased ventilation during and following exercise reduced somewhat the breathing reserve and resulted in an increased tendency to exertional dyspnoea. Dyspnoea had been present in 8 cases prior to thoracoplasty, during the recovery from the standard exercise; for a period of less than two minutes in 4 cases, and more than two minutes in 4 cases. Dyspnoea was present after thoracoplasty in 9 cases; for a period of less than two minutes in 2 cases, and more than two minutes in 7 cases.

Two case reports will illustrate the extreme variations which can be found in this group; the first case showing practically no loss of physical capacity as a result of thoracoplasty, the second case a considerable loss.

Case 1: The patient was a tall, heavy male with a cavity in the left upper lobe. Both his diaphragms had a large excursion (figure 1). The most significant findings following a seven-rib thoracoplasty were as follows (chart 2): (*a*) maximum breathing capacity, very large prior to thoracoplasty, was unchanged after it; (*b*) the ventilation during exercise was greatly increased in the postoperative period; (*c*) the rate of removal of oxygen for each liter of inspired air, both at rest and after exercise, was almost identical to the preoperative value;

[5] Unless otherwise stated, the term "breathing reserve" means "breathing reserve *at rest*."

FIG. 1. Case 1. Roentgenogram taken on deep inspiration before thoracoplasty (to left) and after completion of thoracoplasty (to right). Lines drawn in to show position of chest, heart, mediastinum and diaphragm during expiration (outlined from a separate X-ray plate).

FIG. 2. Case 2. For explanation see fig. 1

FIG. 3. Case 3. See fig. 1

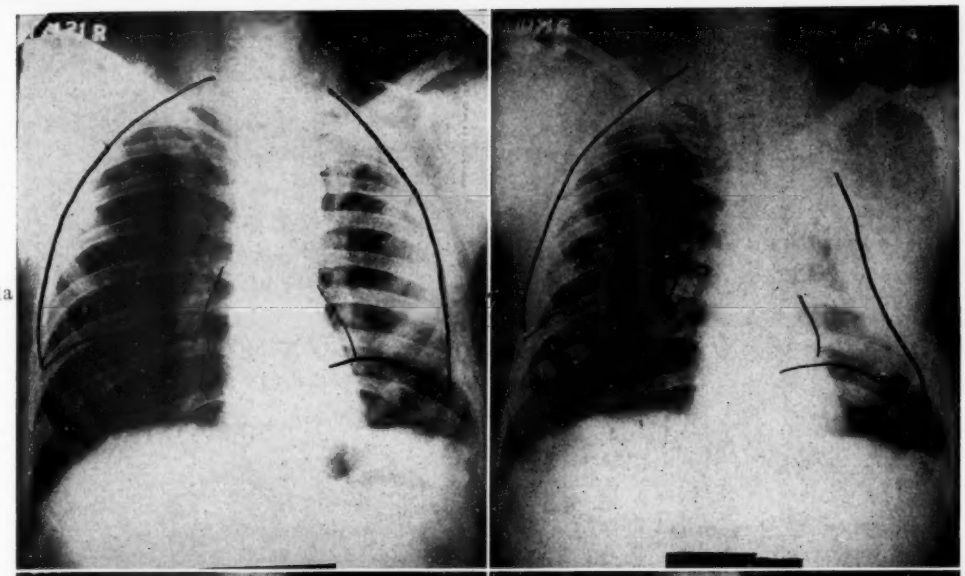


FIG. 1a

FIG. 1b

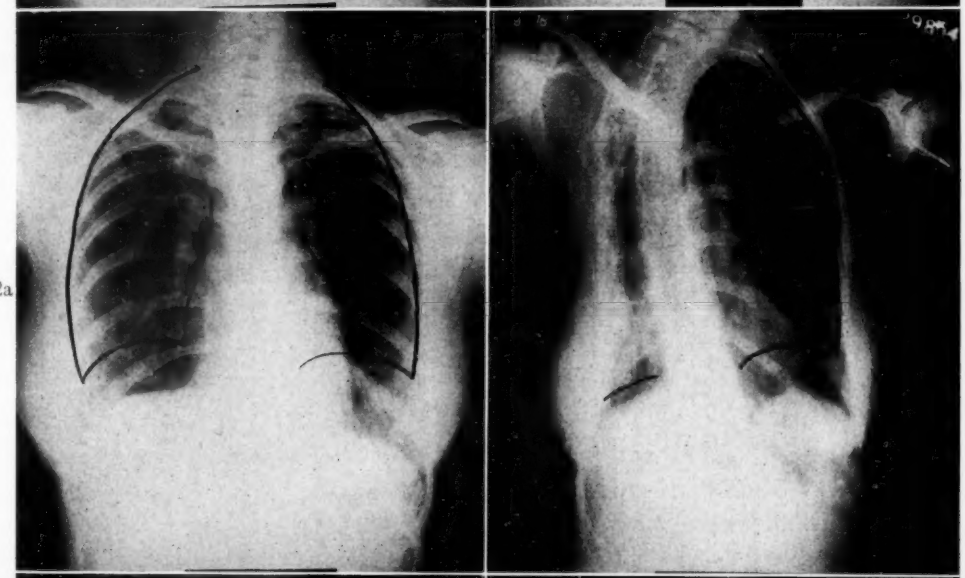


FIG. 2a

FIG. 2b

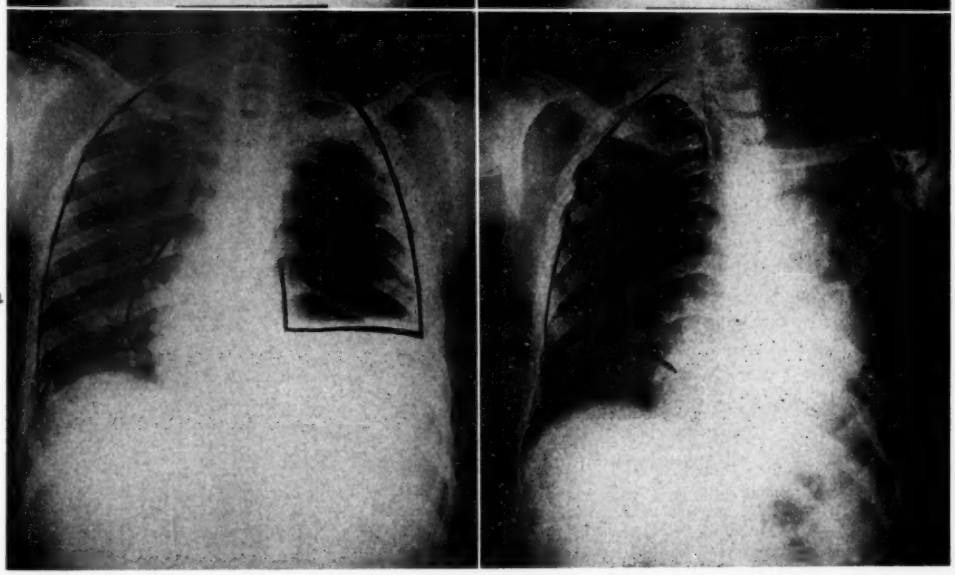


FIG. 3a

FIG. 3b

FIGS. 1a–3b

(*d*) the oxyhaemoglobin saturation per cent, which was below normal figures at rest before thoracoplasty, returned to normal after. Dynamics of circulation, not charted here, showed no departure from normal at any time.

F.Fr. M. 38 Previous Collapse Therapy 0

Duration of Disease 2 ? months Extent of Thoracoplasty 7 upper ribs

	Before	After
Body Surface, sq.m.	1.95	1.94
Sputum	+	0
Physical Activity	Semi-ambulatory	Bed

Interval since last stage 3 months

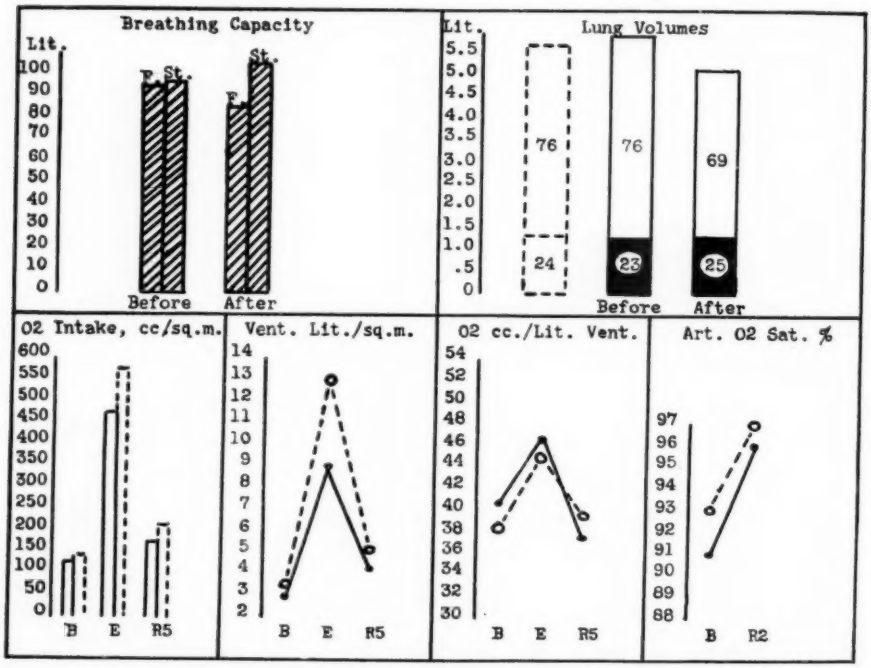


CHART 2. See chart 1 for general explanation of symbols. Breathing capacity = maximum breathing capacity, before and after thoracoplasty; "F." = lying flat; "St." = standing. In Lung Volume chart (as in chart 1) solid block = residual air, white block = vital capacity, dotted line block = "predicted" values. Figure within each block indicates percentage of total capacity; that is, 76 in first upper block indicates that this block (vital capacity) is 76 per cent of the total lung capacity. O_2 intake, cc./sq.m. shows the oxygen intake in cc. per minute per square meter of body surface, under conditions of rest (B), standard exercise (E), and during the fifth minute of recovery from exercise (R5). Solid blocks indicate performance before thoracoplasty, dotted blocks after thoracoplasty. Other charts have the same symbols as in chart 1.

Case 2: A female with a cavity in the upper part of the right lower lobe and good excursion of both diaphragms (figure 2) had a nine-rib thoracoplasty,

following which she developed a marked scoliosis and probably some pulmonary distention in the contralateral lung. In marked contrast to the preceding case (chart 3), her maximum breathing capacity was decreased by 45.2 per cent following operation. Accordingly the breathing reserve at rest decreased from 88.3 per cent to 84.8 per cent of the maximum breathing capacity. With a great increase in ventilation during exercise and recovery, dyspnoea became an outstanding symptom following thoracoplasty, although respiratory gas exchange in the lungs and the state of respiratory gases in the arterial blood remained practically unchanged.

Groups with Total or Partial Artificial Pneumothorax—Groups II and III

Group II—(chart 4): In this group comprising 5 cases, thoracoplasty was performed for the purpose of obliterating the pleural space, with the additional indication of collapsing an apical cavity.

(a) *Preoperative state:* Total lung volume was 63.5 per cent of the predicted value. This was due mainly to a large decrease in vital capacity of 53 per cent of the predicted value. The absolute value of residual air was equal to the predicted value, but with a lung partially or completely collapsed the ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ was 34.4 per cent, higher than normal. Maximum breathing capacity was still large, 67.4 liters per minute, corresponding to 52 per cent of the average maximum breathing capacity in a group of normal subjects with the same sex distribution (see footnote[4]), and the ventilation in liters per minute at rest was larger than in the control group (P between .05 and .02). The breathing reserve at rest was 88.5 per cent of the maximum breathing capacity. The average increase in ventilation during the performance of standard exercise and during the recovery period was sufficiently great to offset the advantage of a relatively good maximum breathing capacity. Thus in 3 cases out of 5, dyspnoea was present during the course of the recovery period for less than two minutes. The rate of oxygen removal per liter of ventilation was higher than in the preceding group, and increased by 5.6 cc. per liter of ventilation during the performance of the standard exercise. Similarly the rate of carbon dioxide output was higher at rest and increased slightly during exercise. Respiratory gases in arterial blood were handled normally, the only abnormal values being a marked increase in blood acidity from a pH of 7.44 to 7.33 during the recovery from exercise, a change probably related to the poor state of physical training of the patients in this group. Venous pressure and circulation time were essentially within normal limits; their changes during the course

of the infusion test and the decrease in vital capacity were also within normal variations.

In summary, there was an expected decrease in vital capacity, a definite increase in the ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ related either to the

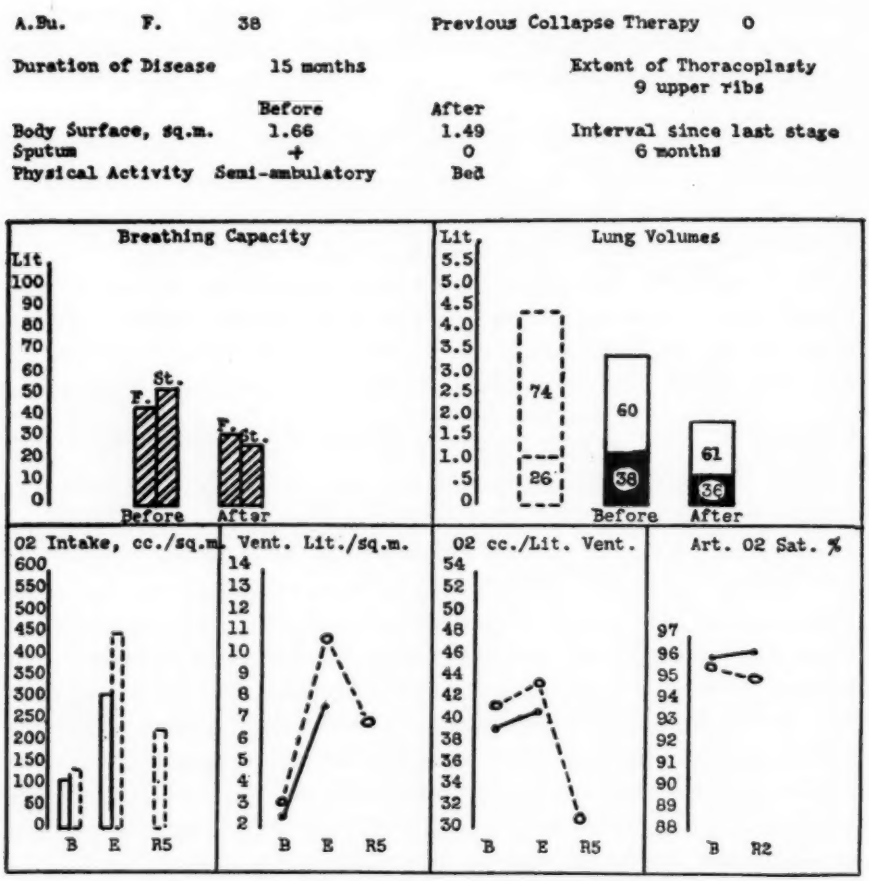


CHART 3. Case 2. See charts 1 and 2

incomplete collapse of an unexpandable lung or to a compensating distention of the contralateral lung, a lower value of maximum breathing capacity and breathing reserve than in normal subjects, and a higher level of ventilation at rest. In other respects, this group prior to thoracoplasty showed essentially normal respiratory and circulatory function.

(b) *Postoperative state:* The postoperative results clearly indicate that

the influence of thoracoplasty, amounting to an average of seven ribs, was in this group practically negligible. The changes in total capacity, vital

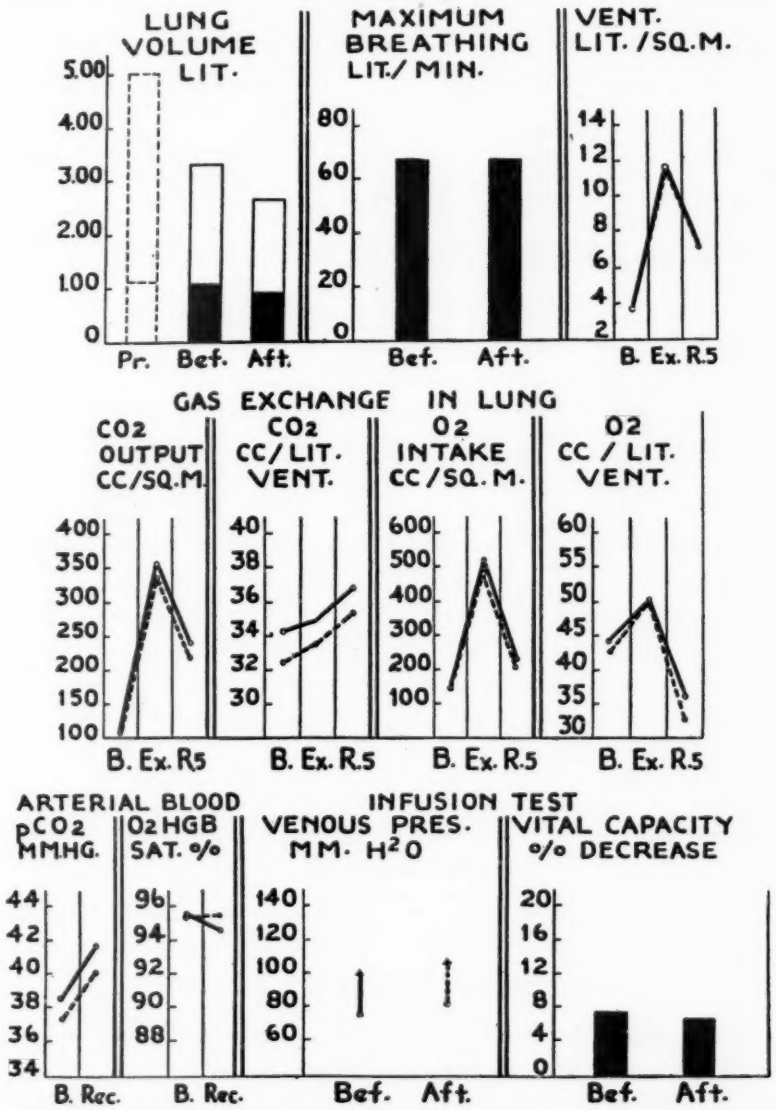


CHART 4. Mean values of principal measurements in 5 patients of group II before and after thoracoplasty. For explanation of symbols see chart 1.

capacity and residual air volume from the preoperative state were found not to be of any statistical significance (P between .4 and .3). Maximum

breathing capacity, breathing reserve and respiratory gas exchange remained what they were before surgery. The state of dyspnoea was unchanged. No evidence of circulatory disturbance was to be found.

P. Pa. M. 22 Previous Collapse Therapy A.P.

Duration of Disease 48 months Extent of Thoracoplasty 8 upper ribs

	Before	After
Body Surface, sq.m.	1.64	1.63
Sputum	±	0
Physical Activity	Bed	Ambulatory

Interval since last stage 32 months

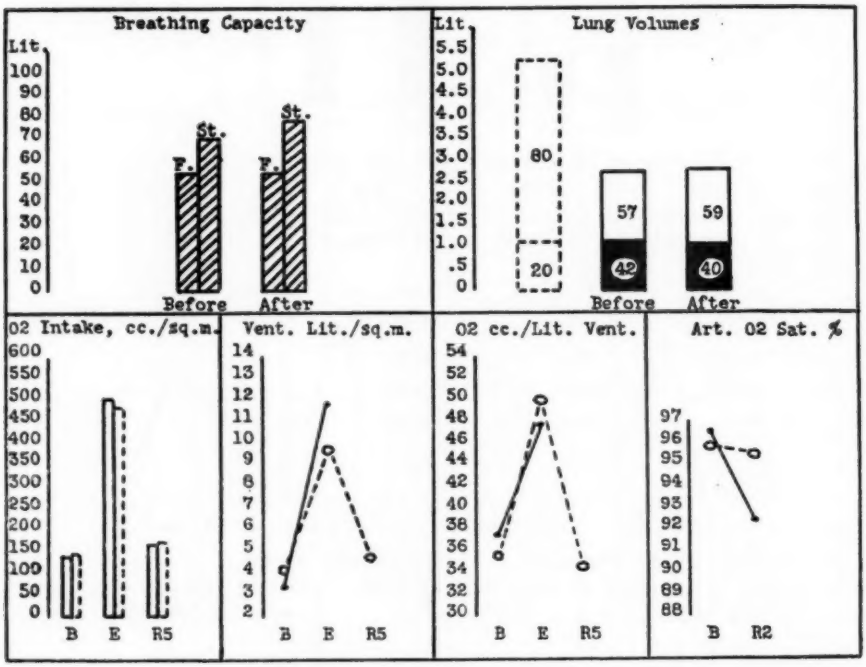


CHART 5. Case 3. See charts 1 and 2

The following case is representative of this group:

Case 3: A young male of twenty-two, after a three-year period of artificial pneumothorax, developed an empyema (figure 3). His sputum was intermittently positive for tubercle bacilli. An eight-rib upper thoracoplasty was performed, which resulted in a complete obliteration of the pleural pocket and a conversion of sputum. The preoperative and postoperative measurements are almost identical (chart 5). The persistence of a high ratio of $\frac{\text{Residual air}}{\text{Total capacity}}$

$\times$ 100 probably indicates that whatever compensating emphysema developed in the contralateral lung was the result of protracted artificial pneumothorax, and not of the surgical collapse. The measurements of circulation, not charted, were and remained within normal limits.

Group III: In the 3 cases of this group, following the resection of an average of 5.7 ribs and collapse of a pneumonic and excavated upper lobe lesion more or less completely adherent, the lower part of the lung was allowed to reëxpand, partially or completely. In contrast to the previous group, total capacity increased by 12 per cent, vital capacity by 16 per cent, and the ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ was reduced. But the most remarkable changes which followed thoracoplasty and reëxpansion of the inefficient pneumothorax were an increase of 50 per cent in maximum breathing capacity and an increase of 3.2 per cent of the breathing reserve at rest. Coincidentally a state of mild dyspnoea, which persisted before operation during the first minute of recovery from standard exercise in all 3 cases, was no longer present following operation.

These findings illustrate strikingly the importance of avoiding unnecessary collapse of normal lung, and the advantage, from the standpoint of physical capacity, of substituting a good thoracoplasty for a poor artificial pneumothorax. A complete study of a case of this group has been presented in a previous report (6), to which the reader is referred.

Reëxpansion of a collapsed lung, either partial or complete, brings in the interesting and practical question of how much such reëxpanded lung tissue can contribute to pulmonary function. Differential bronchoscopy has some of its main indications in such cases. However, useful information can be arrived at without resorting to this technique. The next case is an illustration of this.

Case 4: A young man had a six-rib upper thoracoplasty performed in order to collapse a cavity in the left upper lobe, after failure of an artificial pneumothorax. After successful completion of the thoracoplasty, an attempt was made to reëxpand the lower part of the lung, but this was only partly successful (figure 4). As a result, total lung capacity and maximum breathing capacity increased, but two important physiological changes, not present prior to the attempted reëxpansion, appeared (chart 6): (*1*) the rate of oxygen removal from each liter of inspired air decreased markedly during exercise; (*2*) a tendency to pulmonary congestion was revealed by the infusion test (12 per cent decrease in vital capacity, as against none previous to reëxpansion). Retarded

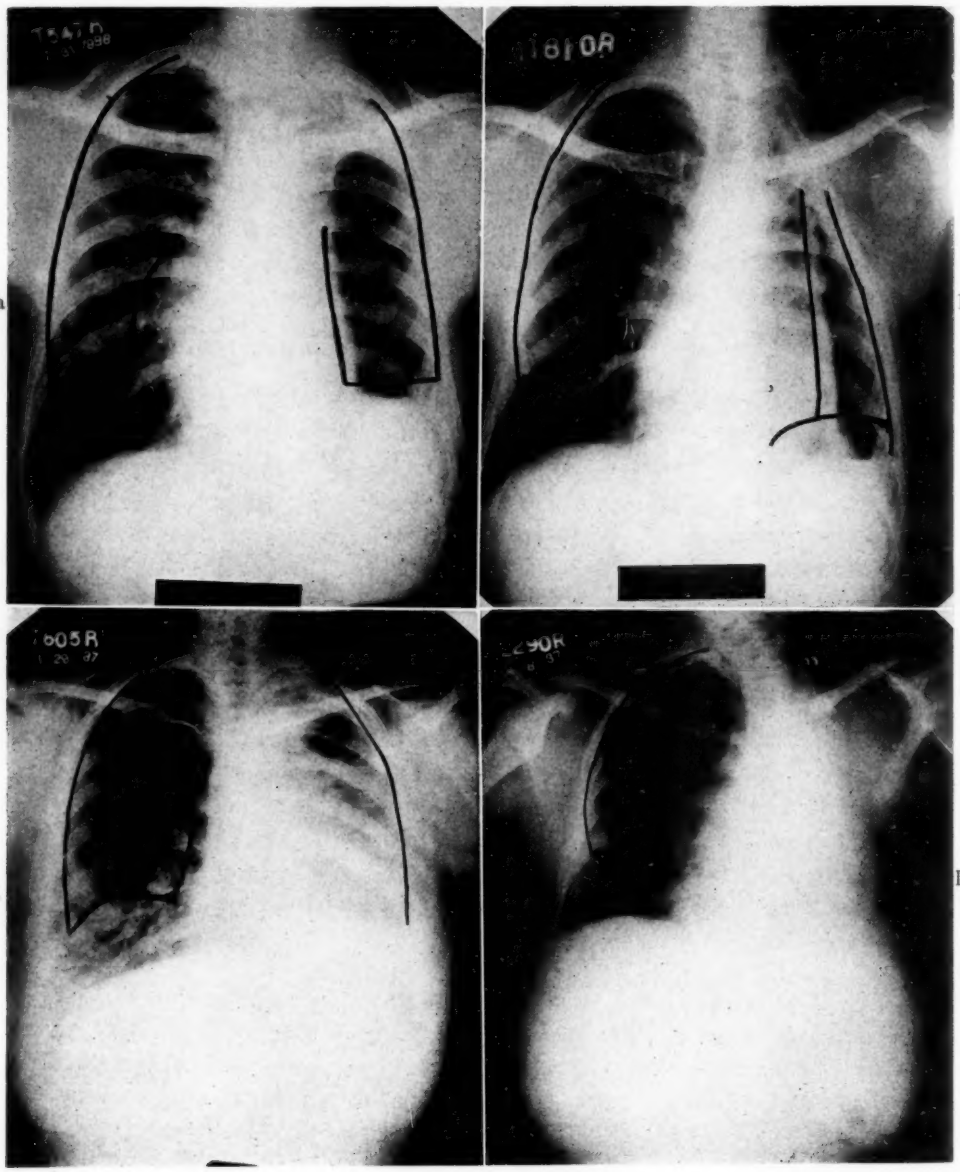


FIG. 4a

FIG. 4b

FIG. 5a

FIG. 5b

FIG. 4. Case 4. See fig. 1
FIG. 5. Case 5. See fig. 1

circulation in the pulmonary capillaries, associated with inefficient ventilation, is suggested by these findings.

Group with Phrenic Paralysis—Group IV (Chart 7)

The 5 cases of this group had a permanent phrenic paralysis on the side on which thoracoplasty was later successfully completed.

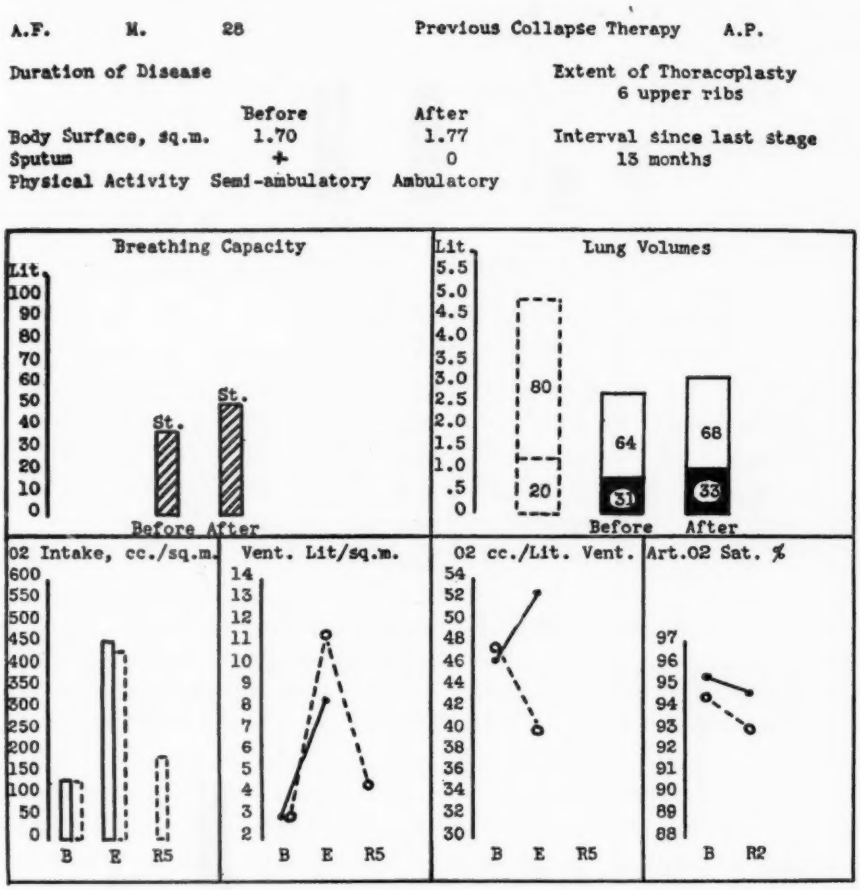


CHART 6. Case 4. See charts 1 and 2

(a) *Preoperative state:* Total capacity of the lungs was 61.6 per cent of the predicted value. This was due to a large decrease in vital capacity, which was 41.8 per cent of the predicted value. Residual air was larger than predicted. Consequently the ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ was high.

Maximum breathing capacity was 44 liters per minute, corresponding to 36 per cent of the average maximum breathing capacity in a group of

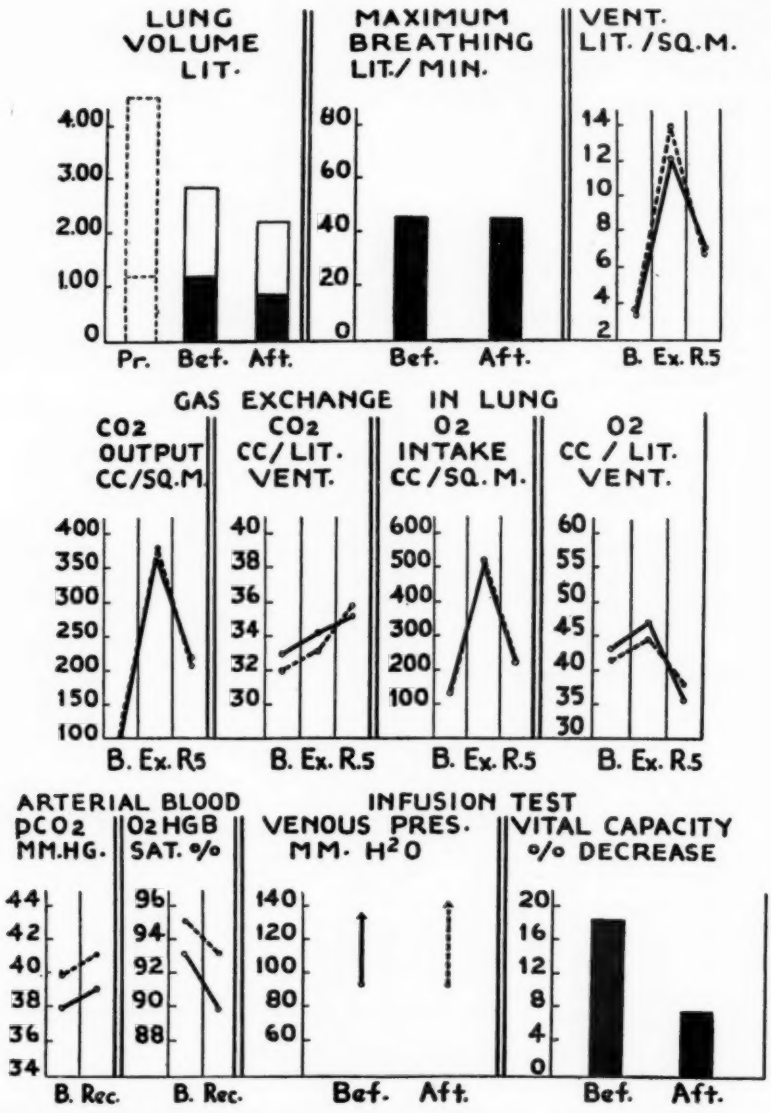


CHART 7. Mean values of principal measurements in 5 patients of group IV before and after thoracoplasty. For explanation of symbols see chart 1.

normal subjects with the same sex distribution (see footnote[4]). Thus in spite of a ventilation at rest not significantly different from normal,

the breathing reserve at rest in the recumbent position was the lowest of all groups studied, 80.6 per cent of the maximum breathing capacity. As a consequence of this low breathing capacity and of a large increase in ventilation during exercise and during the recovery period, 4 out of 5 cases were dyspnoeic during the recovery from exercise for periods of three minutes or more.

The rate of oxygen removal at rest was almost normal, but its increase during exercise was small. Small, too, was the volume of carbon dioxide elimination per liter of expired air, especially at rest.

In the arterial blood, the oxyhaemoglobin saturation of 92.9 per cent was slightly lower than accepted normal values, and still lower after exercise, when it fell to 89.9 per cent. A definite tendency to pulmonary congestion was revealed by the infusion test, which showed a 17.9 per cent decrease in vital capacity at the end of infusion.

Low vital capacity, relatively large residual air volume related either to the presence of a poorly ventilated lung on the side of the paralyzed diaphragm or to compensatory emphysema in the contralateral lung, low breathing reserve, inadequate aeration of the blood and a tendency to congestion in the pulmonary vascular bed were the main abnormal findings in the preoperative state. In short, ventilatory, respiratory and cardiocirculatory insufficiency were present.

(b) *Postoperative state:* Following the resection of an average of 6.8 ribs, the total lung capacity decreased by 23 per cent, vital capacity by only 16 per cent and the residual air by 26 per cent, suggesting that air-bearing lung areas had been collapsed. Maximum breathing capacity in the standing position remained unchanged, but there was an increase in the maximum breathing capacity in the recumbent position. The latter is reflected also in the increased breathing reserve at rest, from 80.6 to 84.5 per cent of the maximum breathing capacity. Exertional dyspnoea was less pronounced in 2 cases, where it lasted only two minutes of the recovery period; 2 cases remained dyspnoeic for the same duration of time; one was not dyspnoeic after exercise either before or following operation. Ventilation and respiratory gas exchange in the lungs were essentially unchanged. Very significant changes in arterial oxyhaemoglobin saturation had taken place; namely, the return of resting values within normal range and an increase of the recovery values to 92.9 per cent of maximum saturation. Venous pressure and circulation time measurements were not different, but following the infusion test the vital capacity decrease amounted to only 7.8 per cent.

These findings suggest (*a*) that as a result of thoracoplasty the mechanics of breathing had not further deteriorated; if anything, improved; (*b*) that, following the collapse of the vascular bed on the side of the thoracoplasty, blood no longer circulated in poorly ventilated lung above the paralyzed diaphragm. The associated tendency to pulmonary congestion had thus been eliminated. This is interpreted as indirect evidence of the damaging effect of phrenic paralysis, at least in the group studied. A remarkable illustration is provided by the following case.

Case 5: An obese woman, thirty-four years of age, with a history of pulmonary tuberculosis dating back nine years, had a large excavation in the left upper lobe (figure 5) which had been unaffected by phrenic exairesis performed three years previously. She was markedly dyspnoeic and cyanotic on the slightest exertion. Her total lung capacity and vital capacity were respectively 55.8 per cent and 36.7 per cent of predicted values, and the ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ was 41.0 (chart 8). Her maximum breathing capacity was very low. Gas exchange was apparently efficiently handled, probably by compensation in the contralateral lung; but the arterial oxyhaemoglobin saturation was low at rest and decreased further following exercise. The circulation time was prolonged and the vital capacity decreased by 24.4 per cent following the infusion test. A ten-rib thoracoplasty was performed from below upward, in order to obtain as complete a collapse of the chest on the left side as possible. This was followed by a striking decrease in the total capacity, solely at the expense of residual air, which constituted then only 31 per cent of the total capacity. Maximum breathing capacity in supine and standing positions increased slightly, and arterial oxyhaemoglobin saturation at rest and following exercise returned to within normal or almost normal range. Venous pressure after the infusion test was increased slightly and vital capacity decreased by 10.6 per cent. Differential bronchoscopy (figure 6) performed after thoracoplasty showed total absence of ventilation on the left side.

Group with Fibrothorax—Group V (Chart 9)

The 5 cases of this group had a marked contraction of one side of the thorax, with the changes usually associated with fibrothorax—immobile and high diaphragm, mediastinal dislocation and hyperinflation of the contralateral lung.

(a) *Preoperative state:* Measurements of pulmonary and circulatory function revealed the following average values: Total lung volume and vital capacity were respectively 74.4 per cent and 53.8 per cent of the predicted values, and the relatively large volume of residual air was

reflected in a ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100 = 38.3$. Maximum breathing capacity was 59.1 liters per minute, corresponding to 48 per cent of the average maximum breathing capacity in a group of normal subjects with the same sex distribution (see footnote[4]); and the breathing reserve at

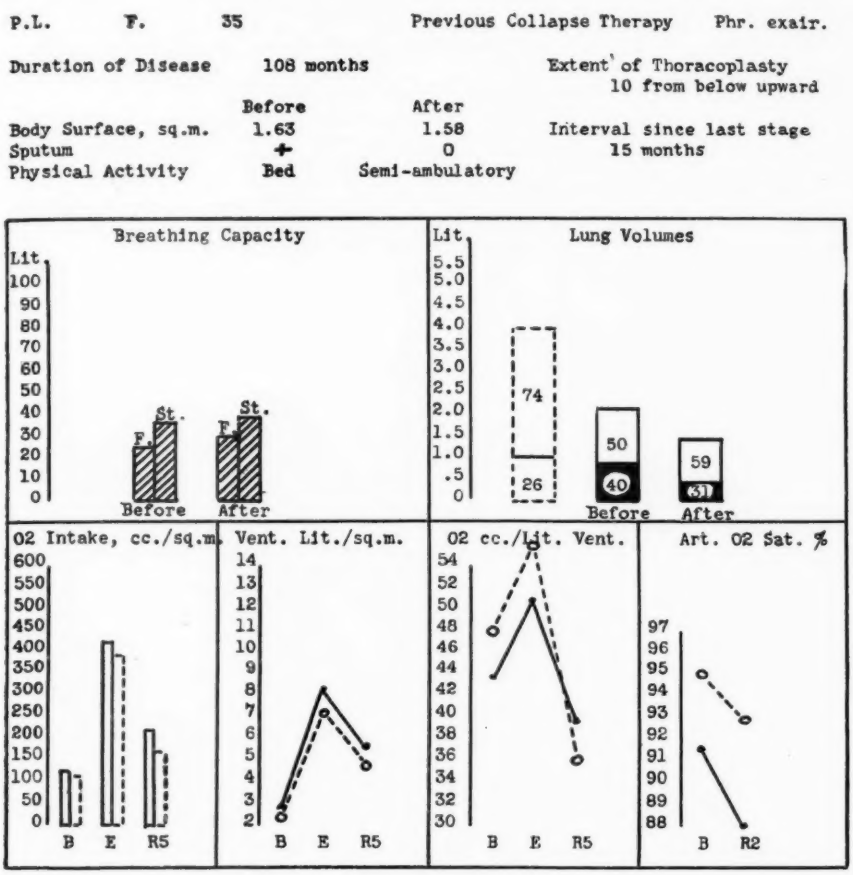


CHART 8. Case 5. See charts 1 and 2

rest was 89.3 per cent of the maximum breathing capacity. Dyspnoea following exercise was present in 3 out of 5 cases for a period of two minutes or less. Ventilation at rest was normal. There was an unusually large increase in ventilation during exercise, associated with a decrease in the rate of oxygen removal from inspired air, and of carbon dioxide output in expired air. In contrast with the group with phrenic

paralysis, however, arterial oxyhaemoglobin saturation was normal at rest and following exercise. A slight tendency to pulmonary congestion

FIG. 6

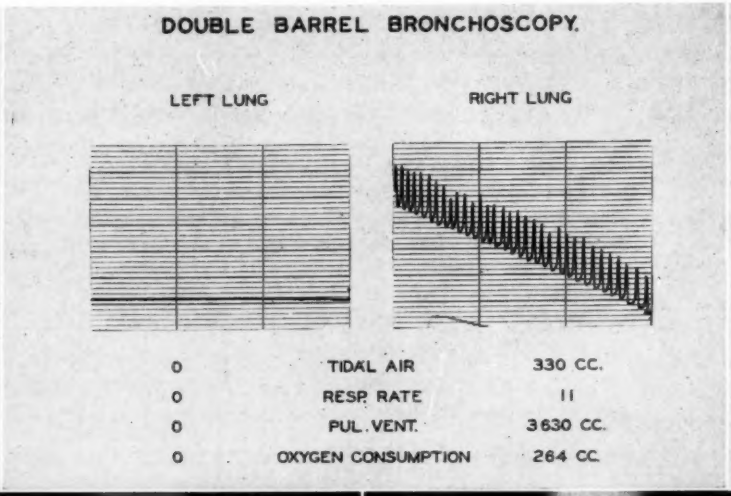
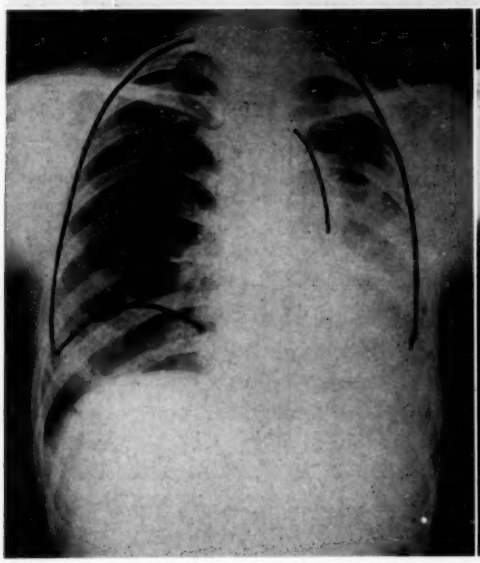


FIG. 7a



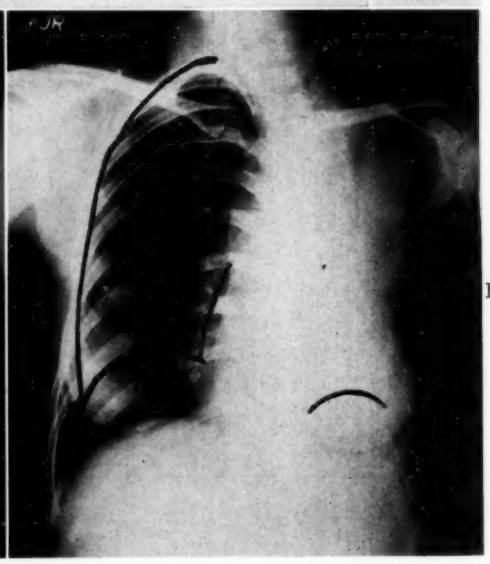


FIG. 7b

FIG. 6. Case 6, after thoracoplasty. Bronchospirometry of each lung separately, showing complete absence of ventilation and oxygen consumption in left lung.

FIG. 7. Case 6. See fig. 1

was revealed by a decrease of 9.2 per cent of the vital capacity following the infusion test.

(b) *Postoperative state:* Resection of an average of 9.9 ribs in this group was accompanied by a proportionally greater decrease in lung volumes

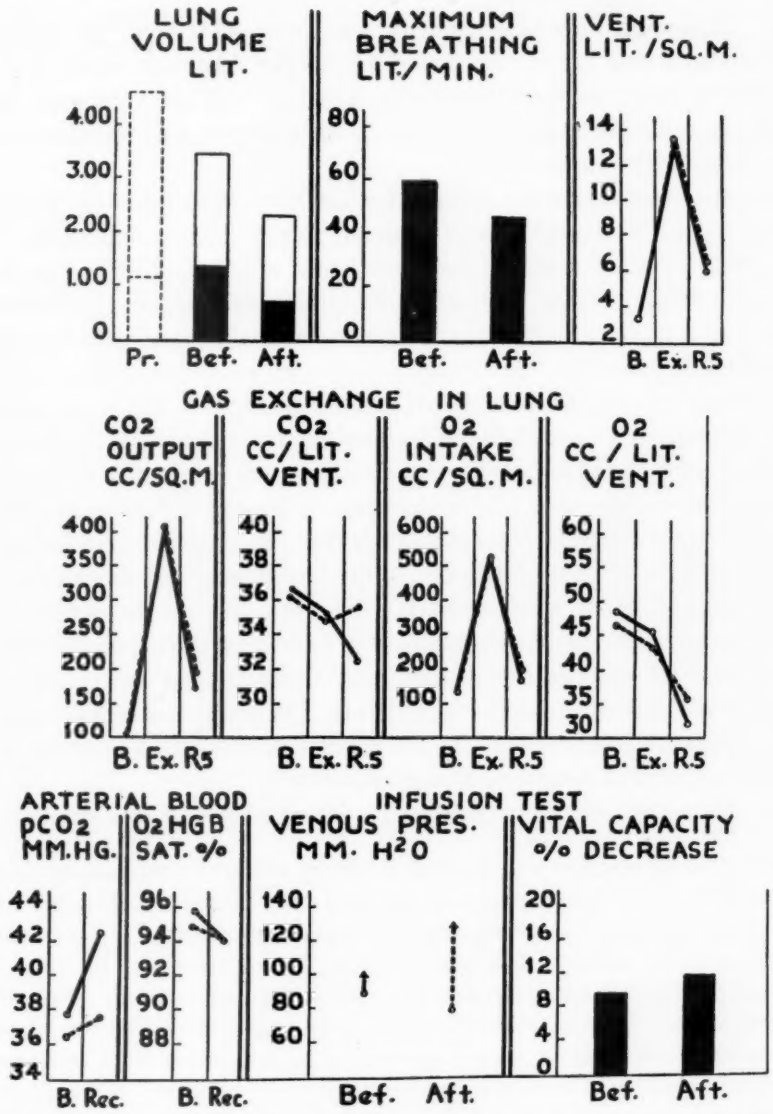


CHART 9. Mean values of principal measurements in 5 cases of group V. For explanation of symbols see chart 1.

than in the first group, where an average of 7.1 ribs were resected. Total capacity decreased significantly by 33 per cent (P between .02 and .01),

vital capacity less significantly by 31 per cent (P between .05 and .02); but the ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ decreased only slightly to 37.1 per cent. Maximum breathing capacity was lower, 45.9 liters per minute, and the breathing reserve decreased by 1.8 per cent to a value of 87.1 per cent of the maximum breathing capacity. All patients were now dyspnoeic following standard exercise, 2 for less than two minutes, 3 for more than two minutes.

All other measurements remained what they were prior to thoracoplasty, but for a slightly greater tendency to pulmonary congestion. In this group some unusual features were found which warrant further discussion; namely, (*a*) the existence before thoracoplasty, and persistence after it, of a decrease in the rate of oxygen removal from inspired air, and of carbon dioxide output in the expired air, with maintenance of a normal arterial oxyhaemoglobin saturation; and (*b*) the slight tendency to pulmonary congestion. To explain the first feature, two hypotheses are offered: (*1*) that owing to the long history of chronic pulmonary tuberculosis, and the marked retraction of half of the chest, a state of diffuse emphysema obtained in the contralateral lung; or (*2*) that ventilated but not perfused lung areas were present on the side of the fibrothorax and persisted after the completion of the thoracoplasty. The presence and persistence of a state of pulmonary congestion might well have been due to displacement and torsion of the heart, with resulting congestion in the pulmonary veins on the side opposite the fibrothorax. Visualization of the pulmonary circulation with diodrast in one patient of this group by Robb and Steinberg (7) gives weight to this interpretation.

The following case shows the changes characteristic of this group.

Case 6: A woman of forty-three, with a history of chronic pulmonary tuberculosis dating back twenty-seven months, had a cavity in a left shrunken lung and a bronchial lesion demonstrated by bronchoscopy (figure 7). The cavity was successfully collapsed following the resection of ten ribs. In chart 10, pre- and postoperative measurements are graphically represented. Following surgery, a great decrease in lung volumes, with slight increase in the relative volume of residual air, is associated with a marked decrease in maximum breathing capacity. There is a large decrease in the efficiency of ventilation with respect to oxygen intake, during exercise prior to thoracoplasty, and still persisting two months after operation, with a normal arterial oxyhaemoglobin saturation. To decide whether this was related to one of the two hypotheses discussed above, a differential bronchoscopy was performed before thoraco-

plasty. It revealed that one-fifth of the total ventilation, with only one-thirtieth of the total oxygen absorption, was taking place on the side of the fibrothorax. Unfortunately it has not been possible, so far, to repeat this mode of exploration since thoracoplasty. It can therefore be stated that direct evidence of the presence of a large pocket of air in a lung still ventilated

A.F. F. 43 Previous Collapse Therapy 0

Duration of Disease 27 months Extent of Thoracoplasty 10 upper ribs

	Before	After
Body Surface, sq.m.	1.51	1.44
Sputum	+	0
Physical Activity	Semi-ambulatory	Bed

Interval since last stage 2 months

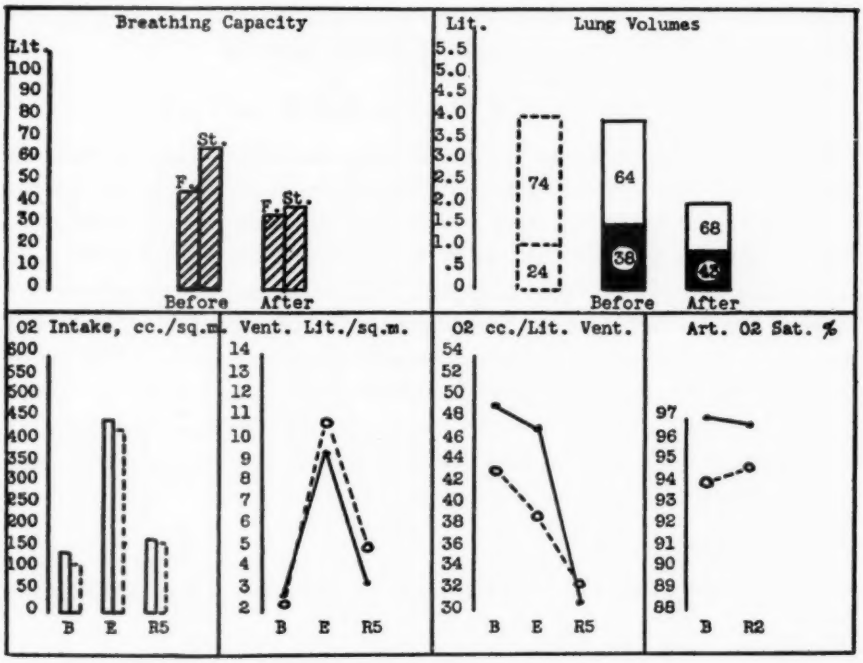


CHART 10. Case 6. See charts 1 and 2

but not efficiently perfused, was found in one case of this group before thoracoplasty.

Extent of Rib Resection and Changes in Lung Volumes and Maximum Breathing Capacity

In order to determine whether a correlation existed between (*a*) the extent of rib resection and (*b*) total capacity and maximum breathing

capacity, 18 cases of groups I and V have been considered; the cases of groups II, III and IV being discarded because, besides thoracoplasty, they presented some additional form of collapse.

The correlation coefficient[6] between the number of ribs resected and the ratio $\frac{\text{Total capacity after thoracoplasty}}{\text{Total capacity before thoracoplasty}}$, $r = +.588 \text{ S.E. } \mp.16$, shows a significant dependence between the two values compared ($P = .01$). The correlation coefficient between the number of ribs resected and the ratio $\frac{\text{Maximum breathing capacity after thoracoplasty}}{\text{Maximum breathing capacity before thoracoplasty}}$ is $r = +.357$ S.E. $\mp.21$, showing no dependence between them (P above .1). On the basis of the latter correlation, no prediction can be made on the effect of thoracoplasty upon the maximum breathing capacity.

Effect of Scoliosis upon Breathing Reserve and Dyspnoea

Five cases of groups I and V developed a moderate degree of scoliosis after thoracoplasty was completed. The breathing reserve at rest in these cases before thoracoplasty was 86.5 per cent of the maximum breathing capacity, as compared with an average value of 87.5 per cent for all the cases in the two groups. The breathing reserve at rest decreased by 5.6 per cent in these cases following operation, while the average decrease for the 18 cases of the two groups was only 2.3 per cent. The effect of this decrease upon exertional dyspnoea was striking. Prior to the thoracoplasty, one of the 5 cases was not dyspnoeic following standard exercise, 4 were dyspnoeic for less than two minutes, while after thoracoplasty all the cases were dyspnoeic for a period of two minutes or more.

B. *State of Pulmonary and Circulatory Function after Therapeutic Phrenic Paralysis (Chart 11)*

Eight cases have been pooled, by adding to the 5 cases of group IV studied before thoracoplasty, 3 cases of phrenic crushing (group VI) in which thoracoplasty was not completed.

The total lung capacity and vital capacity were respectively 59.9 per cent and 40.5 per cent of the predicted value. The ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ was 38.6. Maximum breathing capacity was 50.0 liters per minute,

[6] Calculated by the rank correlation method.

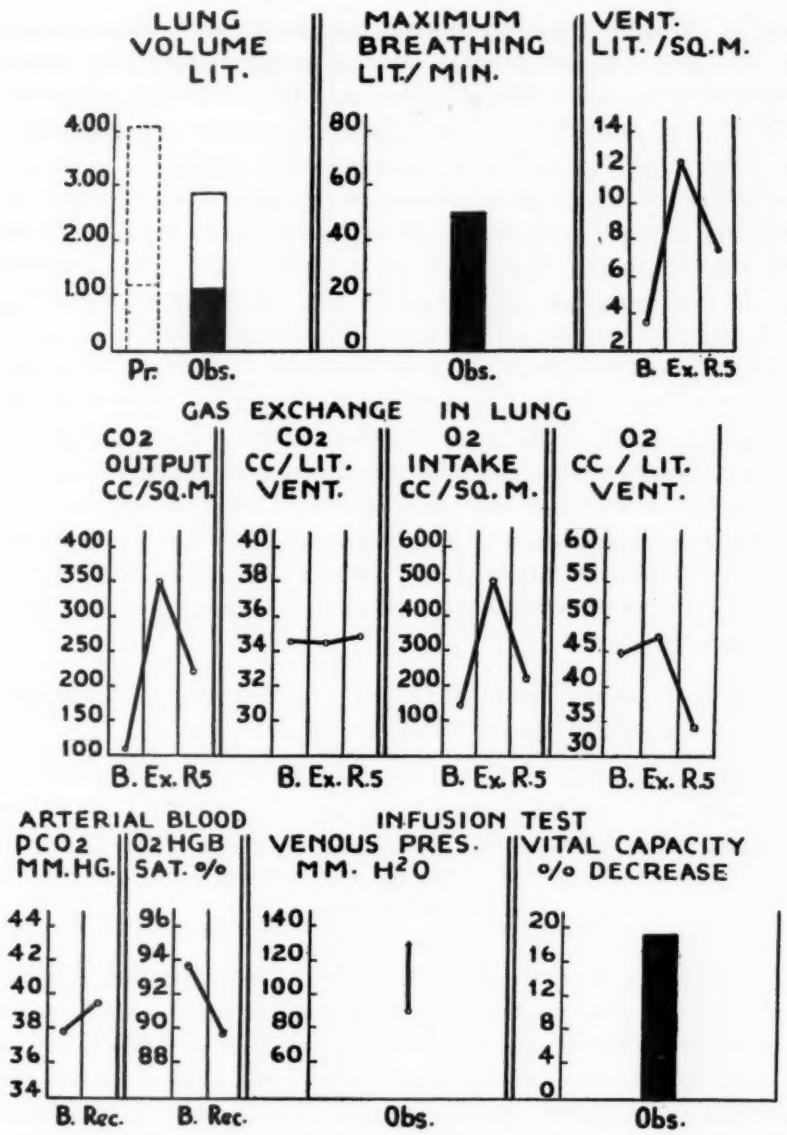


CHART 11. Mean values of principal measurements in 8 cases of therapeutic phrenic paralysis. For explanation of symbols see chart 1.

corresponding to 39 per cent of the average maximum breathing capacity in a normal group with the same sex distribution (see footnote[4]); and the breathing reserve at rest was 82.5 per cent of the maximum breathing

capacity. Whether the interruption of the phrenic nerve is alone responsible for these low figures for vital capacity, maximum breathing capacity and breathing reserve, is difficult to decide, with such a small group where sex distribution and extent of tuberculous lesions might play a significant part. But other data in this group appeared to justify the assumption that therapeutic phrenic paralysis may be detrimental to pulmonary and circulatory function. Ventilation during exercise was much larger than in the control group or in group I prior to thoracoplasty, and coincidentally the rate of oxygen removal per liter of ventilation increased from rest to exercise by only 1.9 per cent. Furthermore, following exercise the arterial oxyhaemoglobin saturation dropped to 89.6 per cent, a value significantly lower ($P = .02$) than the corresponding value in group I after thoracoplasty. Finally a decrease of 19.0 per cent in vital capacity following the infusion test indicates a tendency to pulmonary congestion. Compared to its corresponding value in group I after thoracoplasty, this decrease is highly significant (P less than .01). These findings apparently indicate that phrenic paralysis may result in the persistence of blood circulation in inadequately ventilated lung areas and in a tendency to pulmonary congestion.

C. *State of Pulmonary and Circulatory Function after Reëxpansion of Artificial Pneumothorax—Group VII (Chart 12)*

In this group, comprising 11 cases, artificial pneumothorax had been reëxpanded for a period of time averaging 41.5 months. All patients had resumed normal activity. The total capacity was 80.3 per cent of the predicted value, but the vital capacity was only 66.5 per cent of the predicted value, and the ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ was 34.4, definitely higher than the normal predicted value. The maximum breathing capacity of 60.5 liters per minute corresponded to 53 per cent of the average maximum breathing capacity in a normal group of subjects with the same sex distribution (see footnote[4]). This is the highest relative value for maximum breathing capacity of any of the 7 groups studied, though only slightly larger than group II prior to thoracoplasty. It was desirable to determine whether this measurement was significantly different in this group from similar values in normal subjects and in cases following thoracoplasty. Maximum breathing capacity being significantly different (P lower than .01) in normal males and females, only the larger sex group was considered. The mean value for maximum breathing capacity in

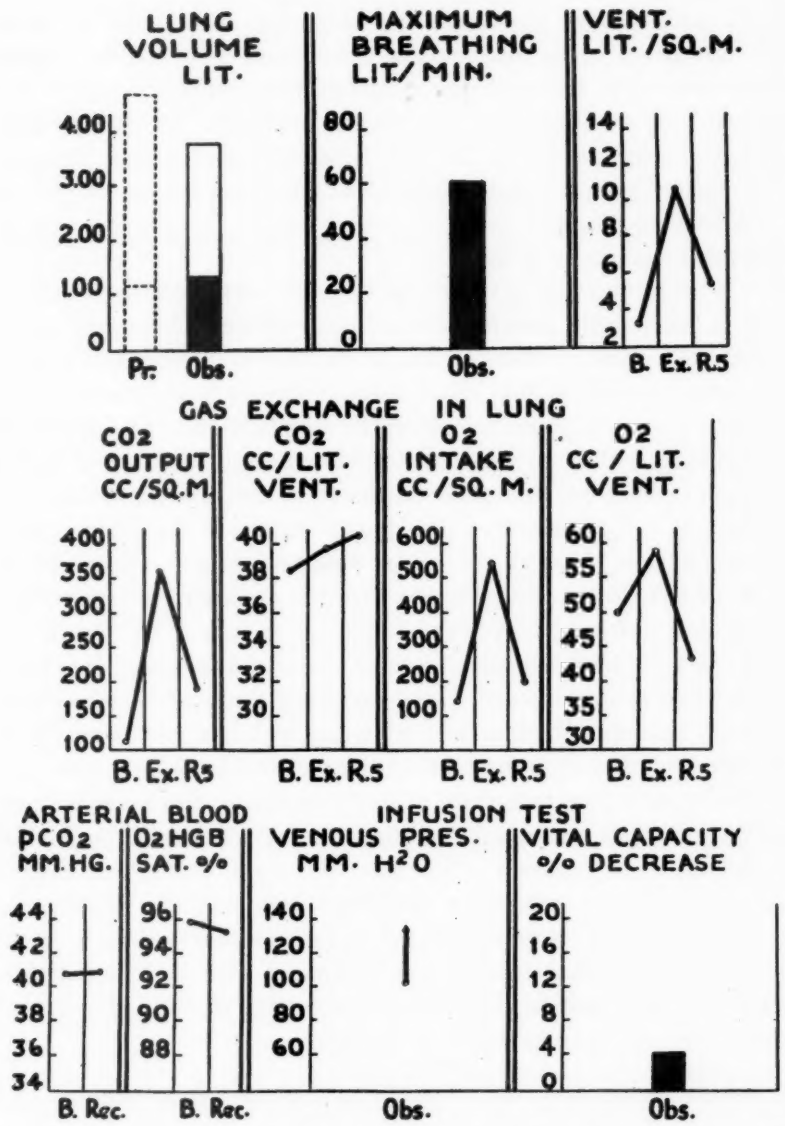


CHART 12. Mean values of principal measurements in 11 cases after reëxpansion of artificial pneumothorax. For explanation of symbols see chart 1.

the 8 females was 57.5 liters per minute. This may be compared with the mean value in normal females, which in a group of 20 was 100.4 liters per minute, and also with that of the 15 females of groups I, II,

III, IV and V after thoracoplasty, which was 41.8 liters per minute. With the group of normal females the difference is highly significant (P less than .01), but with the group of thoracoplasty cases it is just significant (P = .05). With a larger maximum breathing capacity and a lower ventilation at rest, the breathing reserve was higher than in all other groups. If compared to the mean value of the ratio $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ of the 28 cases of groups I ,II, IV and V after thoracoplasty was completed, the corresponding value in the group of reëxpanded pneumothoraces is significantly higher (P between .02 and .01). The normal increase in ventilation during exercise and its rapid return to the normal value during recovery was associated with a total absence of dyspnoea following the standard exercise. Respiratory gas exchange in the lungs was efficiently managed; there was a high rate of oxygen removal per liter of air ventilated at rest, a large increase during exercise and a high rate of carbon dioxide output in the expired air.

In the arterial blood all the values were normal and, in contradistinction to all the groups previously studied, the variations in carbon dioxide tension and pH were very small following exercise. Undoubtedly the better state of physical training was an important factor in the variation of these two measurements. Measurements of circulation revealed an abnormal feature in the form of a relatively high level of venous pressure. Whether this represents mechanical obstruction of the large veins of the circulation, or is due to a state of hypertension in the lesser circulation resulting from an increased resistance to blood flow through fibrotic lungs, is open to question. Whatever its cause, it was not associated with a tendency to pulmonary congestion following the infusion test.

In brief, cases of reëxpanded artificial pneumothorax show a definitely diminished pulmonary function, as compared with normal individuals; though the incapacities are relatively less than in the other groups of chronic pulmonary tuberculosis in this study.

D. *Correlation between Vital Capacity and Maximum Breathing Capacity*

Inspection of figure 8 and figure 9, where individual values of vital capacity and maximum breathing capacity in the 45 cases studied were plotted separately in each sex group, shows the dispersion on both sides of the regression line is greater in the male than in the female group.

Calculating separately for each sex the coefficient of correlation, we found that in the male group r = +.47 S.E. $\mp$.13, and in the female group

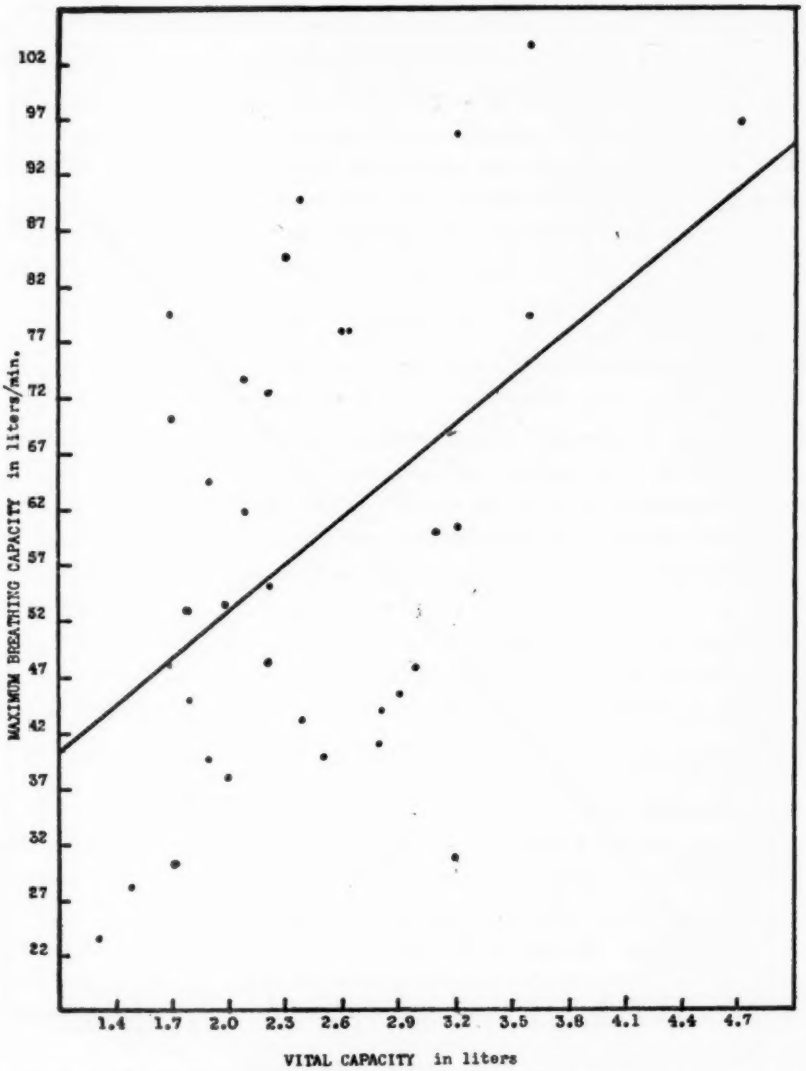


FIG. 8. Correlation between maximum breathing capacity in liters per minute and vital capacity in liters in 35 individual observations made in male patients before or after thoracoplasty. Dots show the scattering of individual observations. Line is regression line of maximum breathing capacity on vital capacity. Correlation coefficient r = +.47 S.E. ∓.13.

r = +.75 S.E. ∓.07. The relation between the two measurements is highly significant (*P* less than .01). It is interesting to note the similarity of the correlation coefficient in the group of male patients and

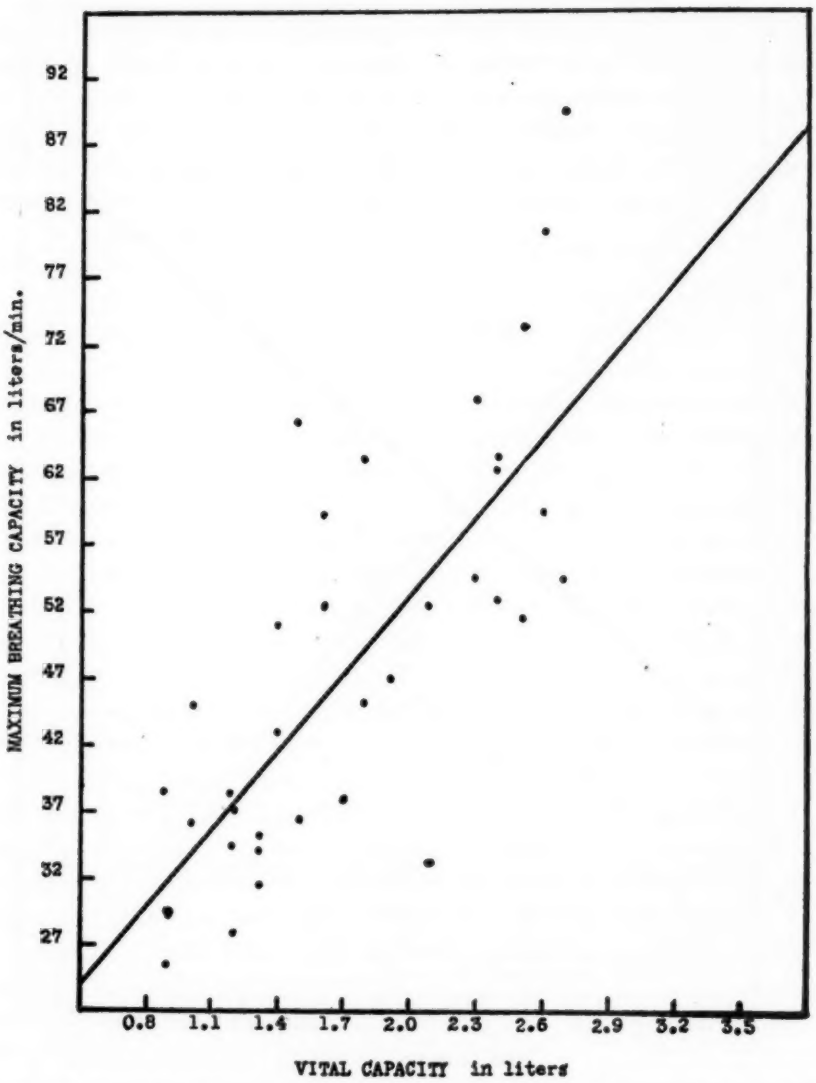


FIG. 9. Correlation between maximum breathing capacity in liters per minute and vital capacity in liters in 34 individual observations made in female patients before or after thoracoplasty. Dots show the scattering of individual observations. Line is regression line of maximum breathing capacity on vital capacity. Correlation coefficient r = +.75 S.E. ∓.07.

normal males, and the more nearly perfect correlation in the group of female patients. Maximum breathing capacity in the latter would appear to depend to a greater extent upon the available lung spaces than

on other factors, among which muscular development, neuromuscular coördination and training might be singled out.

Regression formulae for the calculation of maximum breathing capacity in liters per minute on the basis of the measured vital capacity are for the male group (14.00 × V.C.) + 24.21, and for the female group (19.45 × V.C.) + 14.50. However, in the group of males, prediction of the maximum breathing capacity on the basis of measured vital capacity is not warranted, as the correlation coefficient is far from unity.

DISCUSSION

There have been in the past a limited number of studies dealing with the influence of thoracoplasty upon pulmonary and cardiocirculatory function. In most of them, isolated measurements of lung volumes (8, 9, 10), of venous pressure and circulation time (11), of oxygen debt (12) were made. In few was there an attempt to cover comprehensively the various aspects of pulmonary and circulatory function, and in only rare instances were all measurements duplicated before and after surgical collapse.

In a series of 20 cases, 18 of which were studied only after completion of thoracoplasty, Kaltreider *et al.* (13) found (*a*) the decrease in vital capacity to be greater than expected from the amount of lung collapsed; (*b*) the ratio $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$ to be high; (*c*) a state of anoxaemic anoxia to be present at rest; (*d*) venous pressure to be slightly elevated and blood velocity to be somewhat delayed. Lung volume changes and anoxaemic anoxia were assigned to the considerable impairment of the mechanics of breathing, persisting months after completion of the surgical procedure, which resulted in rigidity of the chest wall and led to unequal alveolar ventilation. The venous pressure and circulation time changes were assumed to be associated with a state of pulmonary congestion developing in the contralateral lung, an observation previously made by MacIntosh in cases studied shortly after operation (14). It is to be noted that in Kaltreider's series the average duration of disease was over ten years, and that in at least 12 cases the extent of rib resection was considerable.

The question of the extent of rib resection is very important, and obviously an apical or subtotal thoracoplasty cannot be compared in its effect to a total thoracoplasty of the Sauerbruch type, or a subtotal posterior thoracoplasty associated with an anterolateral rib resection,

both resulting in considerable collapse, and in most instances in a limitation or elimination of the motion of the diaphragm.

In this respect the conclusions of Gaubatz (15) are very significant. From a study of more than 200 cases with the Knipping spirometer recording (*1*) the maximum breathing capacity and the breathing reserve at rest, (*2*) the oxygen deficit (16), (*3*) the ventilatory equivalent for oxygen (17), this author concludes that an apical thoracoplasty decreases the maximum breathing capacity up to 15 per cent of its preoperative value, an upper type thoracoplasty up to 30 per cent and a subtotal or total up to 40 per cent.

For the first time, the practical value of tests of pulmonary function was studied by Gaubatz who, working with Schmid, attempted to base the choice of the method of collapse, thoracoplasty versus extrapleural pneumothorax, upon these tests. According to him, when maximum breathing capacity is only twice the resting ventilatory volume, thoracoplasty is absolutely contraindicated, and it is only second choice when the maximum breathing capacity is less than 5 times the resting minute volume and when arterial oxyhaemoglobin unsaturation (estimated by measuring the oxygen deficit) is present. There is no mention in this work of the possible beneficial effect of thoracoplasty upon respiratory gas exchange. Yet Decker (18), confirming our findings in one case reported previously (6), has in a small group of patients with phrenic paralysis observed that following thoracoplasty the arterial oxyhaemoglobin saturation tended to return to normal.

By duplicating physiological measurements before and after thoracoplasty, and by grouping our cases according to the same preoperative characteristics, it has been possible for us to show that, to a certain extent, the disability observed after completion of a thoracoplasty is already present before. If one analyzes, for instance, the variations of vital capacity in the different groups, one can see that before thoracoplasty in group I the vital capacity was reduced to 62.9 per cent of the predicted value, in the group of fibrothorax to 53.8 per cent and in the group with diaphragmatic paralysis to barely 40 per cent. Additional percentage decreases from predicted values, due to the thoracoplasty itself, were respectively 15.6 per cent, 16.5 per cent and 6.1 per cent. Similar findings in the variation of maximum breathing capacity confirm the impression that most of its decrease is related to the extent of disease, or to some other type of collapse already present before thoracoplasty. This point of view receives additional support from the finding of a lack

of correlation between the decrease in maximum breathing capacity and the number of ribs resected.

With regard to disturbance in respiratory gas exchange, or evidence of pulmonary congestion, we failed to confirm the findings of Kaltreider *et al.* (13). In our series there was not a single case in which the arterial oxygen saturation was less after operation than it had been before; on the contrary, from a low level before thoracoplasty, the arterial oxygen saturation returned, in some instances, to normal following it. Furthermore, when the infusion test revealed latent pulmonary congestion prior to thoracoplasty, a return to a more normal state of pulmonary circulation was often observed in the postoperative state. The cause of conflicting results in Kaltreider's series might well be found in the long average duration of the disease in that series, the extent of rib resection, in the fact that paralysis of the diaphragm was present in 13 cases and scoliosis developed as a result of operation in 15 cases.

It is quite remarkable that most reports concerning the effect of phrenic interruption upon pulmonary function concur in showing that this operation is often followed by significant physiological changes. Gaubatz (19) states that the vital capacity and the maximum breathing capacity decrease up to 30 per cent, residual air increases markedly, anoxaemic anoxia often develops. Ruttgers and Smilovits (20) likewise stress the unfavorable effect of this type of collapse upon pulmonary function.

Our study of 8 cases gives indirect evidence to support these reports. However, in order to reach indisputable conclusions, it will be necessary to duplicate measurements before and after phrenic nerve interruption in various types of pulmonary lesions, so as to separate the sole influence of phrenic paralysis from the possible cumulative and integrated effects of pulmonary disease, phrenic paralysis and breathing adjustment following it.

In view of the fact that there is considerable literature concerned with the influence of artificial pneumothorax upon lung volumes, gas exchange and pulmonary circulation, it is surprising that so little is known regarding the physiological changes taking place during reëxpansion, and persisting months after complete reëxpansion. As one would expect, during reëxpansion the ventilatory function does improve, and this is clearly shown in the 3 cases of group III; however, the readjustment between local ventilation and local circulation is not always satisfactory and may lead to relative respiratory insufficiency. Of equal interest is the fact, revealed by our study of 11 cases, that at periods many months after

reëxpansion of artificial pneumothorax the ventilatory function is decidedly subnormal. The aetiology of this disability could not be proved and it belongs to future studies to try to differentiate which factors are involved: such as nature and extent of original tuberculous lesions; question of pulmonary fibrosis, developing during collapse; pleural complications; mediastinal displacement or limitation of motion of the diaphragm. The elevated venous pressure seen in this group suggests the possibility of some sort of mediastinal fibrosis, displacement or torsion of the large vessels of the mediastinum, but this has not been proved. In a period when the respective merits of thoracoplasty and artificial pneumothorax are generally debated, it is not without interest to be cognizant of the fact that the physiological capacity of a subject with reëxpanding or reëxpanded lung is usually more or less impaired.

PRACTICAL CONSIDERATIONS

There are a number of practical questions in the solution of which the methods of studying pulmonary and circulatory function here presented may be helpful. These can perhaps be summarized as follows:

1: In cases of disordered preoperative pulmonary function, what type of postoperative pulmonary complications are to be expected?
2: What therapeutic measures are most likely to be helpful during the immediate postoperative course; conversely, what therapeutic measures are contraindicated?
3: Will the physical disability persisting or developing after completion of the thoracoplasty and control of the tuberculous lesions be of such severity as to prevent the return to a mild activity?

To help answer these questions table 3 has been prepared. It includes the principal physiological measurements made in 10 cases out of the 34 cases of this series, in which thoracoplasty was performed. In 7 cases severe or fatal postoperative complications developed; and in 3 additional cases, the state of ventilatory insufficiency persisting or developing was so marked that the patient was more or less completely disabled. With the exception of 5 cases that developed scoliosis following operation, this table includes all patients of the present series with severe dyspnoea present on bed-rest or appearing after mild exertion.

Of 2 postoperative deaths, one was due to infection, the other to the development after operation of an extreme type of paradoxical breathing. It is obvious that in these cases no test of pulmonary or circulatory func-

TABLE 3

Condition before and after operation, in 10 patients who either had severe postoperative complications, or developed persistent ventilatory insufficiency in the late postoperative state

GROUP	NAME	SEX	AGE	MEASUREMENTS BEFORE THORACOPLASTY					POSTTHORACOPLASTY STATE					FINAL CLINICAL CONDITION
						Arterial oxygen saturation per cent				Immediate		Late		
				M.B.C.	$\frac{\text{B.R.}}{\text{M.B.C.}} \times 100$ at rest	Rest	Recovery	Vital capacity per cent decrease after infusion	Intense cyanosis	"Drowned lung"	Severe dyspnoea in bed	$\frac{\text{B.R.}}{\text{M.B.C.}} \times 100$	Dyspnoea*	
				lit./min.										
VI	W. H.	M	26	51.2	88.5	95.2	89.5	−16.4						Death. Infection few days after first stage
VI	K. L.	F	25	51.0	85.0	96.0	88.9	−19.5	Yes	Yes	Yes			Death. Extreme degree of paradoxical breathing few days after first stage
VI	W. C.	M	31	32.9	81.5	92.5	88.8	−25.6	Yes	Yes	Yes			Bed-ridden. Not studied after operation
IV	W. E.	M	52	33.0	79.0	92.9	89.9	−17.1	Yes	No	Yes	78.0	Same	Physical activity very little
IV	S. C.	F	21	18.3	74.8	89.0	88.5	−22.8	Yes	Yes	Yes	82.1	Less	Physical activity mild
IV	D. L.	F	25	34.8	79.3	93.8	86.0	−16.9	Yes	Yes	Yes	83.4	Less	Physical activity moderate
IV	P. L.	F	35	25.5	78.6	91.7	87.8	−24.4	Yes	No	Yes	83.5	Less	Physical activity very little
I	E. M.	F	42	35.8	81.9	93.5	95.1	0	No	No	Yes	80.4	Same	Physical activity mild
I	P. F.	M	34	41.0	80.1	94.4	90.7	−3.5	No	No	Yes	73.0	Greater	Physical activity very little
I	G. S.	M	23	44.0	83.0	95.0	91.8	−4.8	No	No	Yes	77.4	Greater	Physical activity very little

This table includes all cases in this series with severe immediate postoperative complications or with marked ventilatory insufficiency as a late result; except that patients who developed postoperative scoliosis are not included.

* In this column, the degree of dyspnoea after the standard exercise, during the postoperative state, is compared with the dyspnoea following this exercise, before operation.

tion could help predict a fatal outcome, brought about by operative hazard. In the remaining 5 cases with stormy postoperative course, it is significant that the studies made in the preoperative state had shown marked disturbances in pulmonary function. These included (*a*) small maximum breathing capacity, a breathing reserve at rest lower than 82 per cent; (*b*) arterial oxygen unsaturation after exercise; (*c*) tendency to pulmonary congestion as shown by the infusion test.

A proper answer to the second question derives in part from these observations.

(*a*) Regardless of whether a patient is cyanotic or not, and without waiting for the appearance of this ambiguous sign, all patients with a low breathing reserve and an arterial oxyhaemoglobin unsaturation should receive the benefit of oxygen therapy for the purpose of decreasing their minute ventilation and preventing the effects of anoxaemic anoxia, immediately following operation.

(*b*) When latent pulmonary congestion is revealed preoperatively by the infusion test, intravenous injection of large quantities of fluid should be avoided. The severe complications, characterized by the signs of "drowned lung," appeared almost exclusively in the group of patients with diaphragmatic paralysis, who showed evidence of latent pulmonary congestion; and it may well be that thoracoplasty performed from below upward might prevent this complication, as suggested by the results in case P.L.

In answer to the third question, it can be stated that severe ventilatory insufficiency can be expected to persist or develop when the maximum breathing capacity before operation is in males below 45 liters per minute, and in females below 35 liters per minute, and the breathing reserve in both groups below 85 per cent of the maximum breathing capacity. Excepting patients with a lung already completely collapsed by artificial pneumothorax, or with previous diaphragmatic paralysis, it appears that, with a breathing reserve at rest below 85 per cent of the maximum breathing capacity, thoracoplasty should be undertaken with serious misgivings regarding the future activities of the patient. Adams (21) believes that clinical observations alone give significant information regarding this problem. This conclusion, however, was apparently reached solely from a review of the literature, rather than from actual experience in physiological investigation in this field. It has seemed to us that real benefit can be derived from a judicious use of tests of pulmonary function, and this brings up the last question of practical interest: in what patients these tests should be carried out.

Use of these tests is unnecessary in young patients with localized lesions and otherwise apparently good general physical condition. This group forms a large proportion of patients in whom thoracoplasty offers a rapid way of controlling disease, with minimal impairment of pulmonary function. In contradistinction, physiological studies will be of value in patients with (*a*) nodular dissemination, (*b*) repeated haemoptyses in the past, (*c*) protracted disease, (*d*) discrete bilateralization, (*e*) previous collapse therapy, (*f*) finally, in the older age group, where emphysema may be present and cardiocirculatory function may be impaired.

Perhaps the most important feature of the physiological approach which we have attempted is that the entire pulmonary and circulatory behavior of the patient must be viewed comprehensively, if any benefit is to be derived from the study. Little can be gained, in the long run, from measuring one single aspect of the patient's functional behavior and attempting to draw conclusions from this measurement alone.

One additional measurement, which we have referred to only occasionally in the above study, should receive special mention; namely, double bronchospirometry (22) by which the behavior of each lung can be studied separately. This provides a notable addition to the analysis of ventilatory and respiratory behavior. It does not, of course, contribute further to the knowledge of the patient's total pulmonary or circulatory function.

SUMMARY AND CONCLUSIONS

1. The methods of measurement of pulmonary and cardiocirculatory function, described in the preceding paper, have been applied to the study of 45 cases of chronic pulmonary tuberculosis treated with various types of pulmonary collapse.

2. In 31 cases, measurements were made before and again after completion of thoracoplasty. These cases have been subdivided into 5 groups, depending upon the type of disease and the type of therapy (pneumothorax, phrenic paralysis) that existed prior to thoracoplasty.

3. The first group consisted of 13 cases of predominantly unilateral disease, without any previous collapse therapy. In this group there was a considerable decrease in ventilatory function existing before thoracoplasty. There was, in most cases, a moderate further decrease in functional capacity following thoracoplasty (decreased breathing reserve, increased duration of dyspnoea after exercise). In some instances, however, pulmonary and cardiac function were as good after operation as before.

4. The second group comprised 5 cases of long-standing pneumothorax complicated in most instances by empyema. In these cases, pulmonary and circulatory function, determined several months after obliteration of the pleural space by thoracoplasty, were almost identical with these functions prior to surgery.

5. Three cases with partial and ineffective pneumothorax constituted the third group. In 2 of these, after an upper thoracoplasty and reëxpansion of part of the lower lobe, ventilatory function was significantly better than before operation. In the third case, such reëxpansion was hindered by thickened pleura, and in this case some evidence of respiratory insufficiency developed postoperatively.

6. The fourth group was perhaps the most interesting. This consisted of 5 cases with previous permanent diaphragmatic paralysis. In this group, a marked degree of both ventilatory, respiratory and circulatory dysfunction existed before thoracoplasty; all of which were significantly improved, and the patient's physical capacity greater, after completion of thoracoplasty.

7. The fifth group comprised 5 cases of long-standing fibrothorax, with large excavation in the upper half of the lung. A considerable impairment of ventilatory function in this group before operation was increased somewhat further after thoracoplasty. There was also a diminished efficiency of alveolar ventilation. A tendency toward pulmonary congestion in this group (venous pressure increase and vital capacity decrease after intravenous infusion) was thought to be due in part to displacement of the heart and displacement and torsion of the great vessels, especially the pulmonary veins.

8. In general, it can be stated that, in these 31 cases, by far the greater part of the loss of pulmonary function existed prior to thoracoplasty.

9. In groups I and V together, there existed a positive correlation between number of ribs resected and the decrease in the measurement of the static functions, vital capacity and total lung volume; there was, however, no consistent correlation between number of ribs resected and decrease in the dynamic function, maximum breathing capacity. Other important factors disturbing such a correlation in individual cases were the development of scoliosis, further disturbance in diaphragmatic function or collapse of variable amounts of normal lung tissue.

10. A few points of practical interest in connection with operative and postoperative hazard were disclosed by further study of these data: (*a*) When the breathing reserve is less than 85 per cent of the maximum breathing capacity, or when there is significant arterial oxygen unsatura-

tion at rest or after exercise, or when a state of pulmonary congestion develops after the infusion test, then a difficult or stormy postoperative course is likely. (*b*) When the breathing reserve is less than 85 per cent of the maximum breathing capacity, the possible advantages to be gained by thoracoplasty must be weighed against the chances that a further reduction in pulmonary function in the postoperative state may reduce the patient to a permanently incapacitated individual, dyspnoeic on the slightest exertion. Exceptions to this statement may be made in patients who have in the preoperative state a pneumothorax or a diaphragmatic paralysis, since with these conditions pulmonary function is usually as good after thoracoplasty as it was before or actually better.

11. Pulmonary and circulatory function was studied in 8 cases of therapeutic phrenic paralysis. Striking impairment of function was found, as evidenced by (*a*) low ratio of breathing reserve to maximum breathing capacity at rest, (*b*) oxygen unsaturation of arterial blood at rest or after exercise, and (*c*) a distinct tendency to pulmonary congestion after intravenous infusion. While much of this dysfunction may have been due to extensive pulmonary disease, a further effect of phrenic paralysis was suggested by the facts that (*a*) dysfunction was greater than in a comparable group of cases of unilateral disease without phrenic paralysis; and (*b*) pulmonary and circulatory function in the phrenic paralysis cases were usually actually improved following thoracoplasty.

12. In 11 cases of reëxpanded pneumothorax, there was definite evidence of impaired pulmonary function. Maximum breathing capacity was, on an average, larger in this group than in the total group of patients after thoracoplasty. The other notable finding was an abnormally high venous pressure without further evidence of circulatory dysfunction.

13. From the above findings, it is concluded that a comprehensive study of pulmonary and circulatory functions, similar to those used in this investigation, may have practical value, particularly in estimating immediate surgical risk and ultimate physical capacity in patients with definite impairment of function.

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TABLE 4

Lung volume subdivisions

Absolute values in liters and ratio* $\frac{\text{Residual air}}{\text{Total capacity}} \times 100$

GROUP	NUMBER OF CASES	TOTAL CAPACITY†		VITAL CAPACITY‡		RESIDUAL AIR		RESIDUAL AIR / TOTAL CAPACITY × 100	
		Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Thoracoplasty									
Group I before	13	4.26	0.85	2.55	0.72	1.55	0.40	36.8	7.2
Group I after		3.20	0.92	1.92	0.76	1.13	0.24	36.6	6.4
Group II before	5	3.23	0.88	2.11	0.74	1.08	0.31	34.4	8.6
Group II after		2.62	0.82	1.68	0.54	0.88	0.35	33.1	6.1
Group III before	3	2.56	—	1.46	—	1.06	—	41.0	—
Group III after		2.86	—	1.70	—	1.08	—	38.1	—
Group IV before	5	2.79	0.68	1.38	0.35	1.12	0.23	40.6	2.1
Group IV after		2.16	0.81	1.17	0.41	0.82	0.35	37.3	3.7
Group V before	5	3.44	0.35	1.88	0.31	1.31	0.24	38.3	7.1
Group V after		2.31	0.45	1.31	0.27	0.86	0.22	37.1	7.3
Phrenic paralysis	8	2.91	0.67	1.54	0.41	1.11	0.21	38.8	3.9
Reëxpanded artificial pneumothorax	11	3.78	0.62	2.35	0.43	1.30	0.33	34.1	4.6

* Volume of gas calculated at 37°C., prevailing barometric pressure, and saturated with water.

† Total capacity obtained by adding complementary air, reserve air, and residual air measured separately.

‡ Vital capacity as observed.

TABLE 5

Maximum breathing capacity in liters per minute and ratio* $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$ *at rest†*

GROUP	NUMBER OF CASES	MAXIMUM BREATHING CAPACITY		RATIO $\frac{\text{BREATHING RESERVE}}{\text{MAXIMUM BREATHING CAPACITY}} \times 100$	
		Mean	Standard deviation	Mean	Standard deviation
Thoracoplasty					
Group I before	13	53.8	17.0	86.8	5.0
Group I after		45.1	21.4	84.4	6.8
Group II before	5	67.8	21.9	88.5	3.4
Group II after		67.2	23.0	88.7	3.4
Group III before	3	38.5	—	84.8	—
Group III after		57.7	—	88.0	—
Group IV before	5	44.0	19.1	80.6	6.3
Group IV after		43.4	16.3	84.5	3.0
Group V before	5	59.1	14.1	89.3	2.1
Group V after		45.9	8.0	87.1	2.6
Phrenic paralysis	8	50.0	20.0	82.5	5.0
Reëxpanded artificial pneumothorax	11	60.5	19.2	89.5	4.3

* Standing.

† Breathing reserve is the difference between ventilation in liters per minute and the maximum breathing capacity, both measured supine, under basal metabolic conditions.

TABLE 6

Ventilation at rest, during exercise, and during fifth minute of recovery

GROUP	NUMBER OF CASES	VENTILATION, LIT./MIN. PER SQ.M. B.S.*					
		Basal		Exercise		Recovery 5	
		Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Thoracoplasty							
Group I before	13	3.74	.62	10.52	1.81	6.14	1.11
Group I after		3.65	.50	11.97	1.92	6.21	.62
Group II before	5	3.64	.50	11.66	2.20	7.35	1.50
Group II after		3.76	.61	11.37	1.32	7.05	1.20
Group III before	3	3.58	—	10.81	—	—	—
Group III after		3.45	—	11.50	—	—	—
Group IV before	5	3.53	.41	12.11	3.23	7.00	.55
Group IV after		3.58	.53	12.55	4.43	6.61	2.00
Group V before	5	3.32	.15	13.02	1.27	6.04	.81
Group V after		3.34	.40	13.41	.75	6.25	1.41
Phrenic paralysis	8	3.53	.45	12.12	2.57	7.24	.33
Reëxpanded artificial pneumothorax	11	3.16	.48	10.47	1.20	5.27	1.86

* Saturated gas at 37°C. and prevailing barometric pressure.

TABLE 7

Respiratory gas exchange: oxygen intake

GROUP	NUMBER OF CASES	O_2 INTAKE, CC./MIN./SQ.M. B.S.*						O_2 INTAKE, CC./LIT. VENTIL.					
		Basal		Exercise		Recovery 5		Basal		Exercise		Recovery 5	
		Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Thoracoplasty													
Group I before	13	134	18.8	444	58.9	193	41.6	40.9	4.1	47.9	5.7	35.9	5.9
Group I after		130	12.7	487	71.1	167	26.8	40.4	4.0	46.3	7.0	30.6	5.0
Group II before	5	142	10.2	513	91.4	232	42.5	44.4	4.4	50.0	4.1	35.8	2.3
Group II after		140	10.2	483	82.3	203	22.3	42.4	4.0	48.3	4.8	32.7	3.3
Group III before	3	135	—	448	—	—	—	42.9	—	47.1	—	—	—
Group III after		136	—	460	—	—	—	44.9	—	45.6	—	—	—
Group IV before	5	133	4.3	498	89.2	220	35.2	43.2	3.0	46.7	5.4	35.8	3.1
Group IV after		131	7.8	509	94.8	219	26.4	41.5	6.3	44.6	8.3	37.6	3.2
Group V before	5	141	6.5	516	58.4	170	22.3	48.5	1.6	45.2	3.6	31.9	3.7
Group V after		136	15.9	518	50.1	196	23.5	46.2	3.1	43.9	4.2	35.7	6.2
Phrenic paralysis	8	139	16.9	498	73.6	216	27.0	44.8	3.6	46.7	5.2	33.9	6.8
Reëxpanded artificial pneumothorax	11	139	16.9	537	98.6	199	38.7	50.0	8.2	58.2	8.9	42.9	10.7

* Dry gas at 0°C. and 760 mm. Hg.

TABLE 8

Respiratory gas exchange: carbon dioxide output

GROUP	NUMBER OF CASES	CO_2 OUTPUT, CC./MIN./SQ.M. B.S.*						CO_2 OUTPUT, CC./LIT. VENTIL.					
		Basal		Exercise		Recovery 5		Basal		Exercise		Recovery 5	
		Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Thoracoplasty													
Group I before	13	104.1	12.8	313	53.3	198	29.2	31.9	3.2	33.8	4.3	36.8	3.3
Group I after		101.4	10.4	346	39.0	186	18.6	31.6	2.3	32.9	3.6	34.1	2.8
Group II before	5	109.0	9.7	353	66.0	238	52.5	34.2	2.5	34.8	2.9	36.7	3.5
Group II after		107.0	9.1	336	48.7	219	28.2	32.4	2.8	33.5	2.4	35.3	4.7
Group III before	3	101.1	—	311	—	—	—	32.5	—	32.9	—	—	—
Group III after		101.2	—	322	—	—	—	33.3	—	31.4	—	—	—
Group IV before	5	102.5	5.0	363	35.9	216	—	32.9	1.7	34.1	1.5	35.1	—
Group IV after		101.0	5.8	377	68.1	208	—	32.0	4.3	33.0	3.8	35.7	—
Group V before	5	106.0	4.6	403	44.5	171	28.1	36.5	1.0	35.2	1.8	32.2	3.7
Group V after		106.0	11.6	408	47.3	195	48.7	36.1	2.7	34.6	2.6	35.5	3.7
Phrenic paralysis	8	107.0	—	366	—	221	—	34.4	3.0	34.3	5.1	34.7	1.5
Reëxpanded artificial pneumothorax	11	107.0	12.4	366	39.6	187	55.4	38.3	4.5	39.7	5.5	40.4	5.5

* Dry gas at 0°C. and 760 mm. Hg.

TABLE 9

Arterial blood: oxygen capacity and oxygen saturation per cent at rest and during recovery from standard exercise

GROUP	NUMBER OF CASES	OXYGEN CAPACITY, VOLS. %				OXYGEN SATURATION, %			
		Rest		Recovery		Rest		Recovery	
		Mean	Variation	Mean	Variation	Mean	Standard deviation	Mean	Standard deviation
Thoracoplasty									
Group I before	13	17.9	14.9–21.9	18.8	16.5–22.9	94.0	2.1	94.5	2.1
Group I after		17.9	15.9–22.2	18.9	16.9–22.8	94.5	1.9	94.8	2.6
Group II before	5	18.3	15.4–22.2	19.9	16.3–23.5	95.5	.9	94.6	3.2
Group II after		17.3	10.8–21.7	18.2	11.6–22.6	95.3	.8	95.4	1.7
Group III before	3	19.2	18.2–20.8	19.9	18.7–21.5	94.1	—	92.5	—
Group III after		20.6	20.2–21.2	22.1*	—	95.5*	—	94.9*	—
Group IV before	5	18.3	16.8–20.8	19.9	17.6–22.9	92.9	2.9	89.9	4.4
Group IV after		16.8	12.8–19.5	17.9	13.6–20.3	95.0	1.7	92.9	4.0
Group V before	5	16.5	14.3–18.9	17.5	15.4–19.6	95.7	1.3	93.9	1.8
Group V after		16.6	15.0–17.2	17.4	16.1–18.5	94.8	.9	93.9	1.6
Phrenic paralysis	8	18.7	15.3–21.7	20.1	16.7–22.9	93.5	2.7	89.6	3.2
Reëxpanded artificial pneumothorax	11	17.1	16.0–21.5	18.2	16.5–22.7	95.8	1.6	95.1	2.4

* Two cases.

TABLE 10

Arterial blood: carbon dioxide content, carbon dioxide pressure, and pH at rest and during recovery from standard exercise

GROUP	NUMBER OF CASES	CARBON DIOXIDE CONTENT, VOLS. %				CARBON DIOXIDE PRESSURE, MM. Hg				pH			
		Rest		Recovery		Rest		Recovery		Rest		Recovery	
		Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Thoracoplasty													
Group I before	13	49.5	2.8	45.5	3.1	39.1	3.2	41.9	4.5	7.43	.01	7.36	.03
Group I after		48.6	3.2	44.4	4.1	38.1	3.4	41.6	5.8	7.43	.03	7.37	.02
Group II before	5	48.2	2.6	42.5	2.2	38.3	2.8	41.6	3.1	7.44	.01	7.33	.03
Group II after		48.1	2.3	42.6	4.2	37.2	.5	39.9	2.2	7.45	.01	7.36	.03
Group III before	3	46.5	—	43.2	—	34.7	—	40.3	—	7.46	—	7.37	—
Group III after		44.6	—	42.0	—	34.1	—	36.1	—	7.46	—	7.44	—
Group IV before	5	48.2	3.1	43.4	3.9	37.8	3.4	38.9	7.6	7.45	.02	7.39	.02
Group IV after		51.2	3.6	45.2	4.1	39.8	3.0	41.0	8.2	7.45	.02	7.38	.04
Group V before	5	49.1	2.2	44.6	2.0	37.7	2.9	42.3	2.9	7.44	.03	7.35	.02
Group V after		47.6	2.4	42.7	1.3	36.4	1.5	37.5	4.5	7.44	.01	7.38	.06
Phrenic paralysis	8	48.2	2.2	43.3	3.7	37.8	2.4	39.4	7.1	7.45	.03	7.38	.06
Reëxpanded artificial pneumothorax	11	48.5	3.6	45.7	4.3	40.7	2.8	40.9	4.3	7.43	.02	7.41	.03

TABLE 11

State of circulation: venous pressure, circulation time before and at end of infusion of 1,500 cc. of saline in thirty minutes. Per cent decrease in vital capacity following infusion

GROUP	NUMBER OF CASES	VENOUS PRESSURE, MM. H_2O				CIRCULATION TIME, SEC.				VITAL CAPACITY, % DECREASE	
		Before infusion		At end of infusion		Before infusion		At end of infusion		At end of infusion	
		Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation
Thoracoplasty											
Group I before	13	63.4	31.7	96.2	27.6	18.5	2.1	18.7	2.9	4.3	1.3
Group I after		66.5	26.6	116.9	28.5	17.1	3.8	17.6	3.9	4.1	3.3
Group II before	5	76.2	15.4	100.3	17.0	15.3	—	14.3	—	7.2	4.1
Group II after		80.0	13.5	106.5	46.7	18.0	3.4	18.7	2.8	6.4	5.9
Group III before	3	61.7	—	112.3	—	—	—	—	—	—	—
Group III after		100.3	—	125.7	—	—	—	—	—	—	—
Group IV before	5	94.3	27.7	135.0	20.1	19.5	5.3	17.3	—	17.9	7.7
Group IV after		93.3	23.1	141.5	20.8	17.8	3.6	15.7	—	7.3	5.7
Group V before	5	88.0	24.6	101.4	19.0	14.4	3.7	17.8	1.9	9.2	3.9
Group V after		78.4	23.6	129.0	37.6	18.4	3.5	21.3	2.2	11.4	7.0
Phrenic paralysis	8	89.9	32.7	131.4	20.2	17.9	4.4	17.0	2.5	19.0	6.2
Reëxpanded artificial pneumothorax	11	100.9	32.2	133.6	20.6	15.6	2.6	15.3	4.2	4.0	4.2

COLLAPSE THERAPY IN MODERATELY ADVANCED TUBERCULOSIS[1]

An Inquiry into Case Selection and a Statistical Study of End Results

K. M. SODERSTROM[2]

The passing of time changes much of our basic knowledge in therapy. To-day we are not as positive in our statements regarding the effect or force of collapse therapy on tuberculosis as a disease, as we were a few years ago. Justifiable questions have arisen from time to time as to the true merit of collapse therapy. Reporting late effects and complications due to collapse procedures has in recent years made many clinicians less optimistic for those procedures than they were a decade or more ago. This paper attempts to study the question in an unbiased manner from statistical material covering a five-year post-sanatorium follow-up of tuberculosis cases. The ardent exponent of collapse therapy may dislike the findings and take issue with the method of study. The clinician reservedly opposed to collapse therapy is apt to agree in detail with this study. Neither is justified because no compilation of statistics on collapse therapy exists to-day that does not have some impurity in it. An unbiased study may, however, sift enough truth from such statistics to make them of some value. All too often when a statistical study has been made on this subject, preconceived ideas have apparently biased the study. Conclusions have been drawn from impure and noncomparable data in ways that make the bias quite apparent. This is always unfortunate as it fogs, if not destroys, the study. There has yet to appear in the medical literature a statistical study on collapse therapy that can totally withstand the honest criticism of an impartial biostatistician. Indeed, when in Great Britain a few years ago (1) a commission reported several years of statistical study on the evaluation of pneumothorax, it became apparent to the world that a completely sound statistical approach to the collapse problem could not be made. To collect statistical data, a prearranged methodology must be created if the

[1] Study made at Trudeau Sanatorium, Trudeau, New York.

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ideal study is to be made. This, of course, was not done in the first years of employing collapse therapy. The writer has been unable to find that even at this late date an adequately prearranged and controlled method has been formulated preparatory to the evaluation of any of the collapse techniques. The findings submitted in this paper constitute a hindsight study rather than one prepared by foresight. It is admittedly open, as are other similar studies, to statistical criticism but is offered with the hope that it will be of some value to those interested in this subject and who are concerned with it from an unprejudiced point of view.

To Drs. Fred Heise and Homer Sampson of Trudeau Sanatorium, the writer is indebted for the use of the record material in this study. It is well known that the Trudeau Sanatorium has some of the most valuable tuberculosis follow-up records in existence and that from these have come some valuable tuberculosis studies. This study was made at the Sanatorium during the month of June, 1940.

SELECTION OF MATERIAL FOR STUDY

In this analysis it was decided to use the moderately advanced cases for two reasons. First, because they comprised the majority of the total cases admitted to the Sanatorium over the time period when collapse therapy was on the ascendency. Second, because very few of the minimal cases were given collapse therapy and at the same time the majority of the far advanced cases were so treated. Under no conditions could these three classifications be pooled and used as pure statistical data. For many reasons it is impossible to get strictly homogeneous statistical material even from the moderately advanced group. However, by limiting the study to this group some semblance of case-specific rates can be derived.

As a whole, the moderately advanced case has a fairly good outlook. However, his future is probably more determined by therapy, or the lack of it, than is the minimal or the far advanced case. This should be particularly true when measured over a span of post-sanatorium years. It cannot be said that the moderately advanced case is either hopeless from the first diagnosis or is amenable to any choice of therapy. For the above reasons the moderately advanced cases were chosen for study.

To allow for all cases to have been out of the Sanatorium for at least five years, all case records were taken between the dates of admission, July, 1927 and October, 1933, which amounted to exactly 1,500, and the moderately advanced cases selected from these. Of this total, 821, or

55 per cent, were found to have been classified as moderately advanced. Table 1 reveals the number of cases given collapse measures and the method used. Because none of these cases received major chest surgery while classed as first admissions, they are grouped simply as collapse or noncollapse, moderately advanced cases. The question presented in this paper is that of the value of collapse therapy in this type of case; thus the rational for mixing pneumothorax with a few phrenic interruption procedures. Physicians who champion the choice of one of these procedures over the other will object to this mixture, but the fact remains that the majority of clinicians use one procedure as an alternative to the other and this alone justifies placing them on a level for this study.

To secure a random sample of cases treated with no collapse for equal comparison with those so treated, the following sampling method was

TABLE 1

Types of collapse therapy, moderately advanced cases—July, 1927 to October, 1933

TYPE OF COLLAPSE	NUMBER OF CASES
Pneumothorax	170
Phrenic interruption	22
Pneumothorax and phrenic interruption combined	9
Thoracoplasty and other	0
Total	201

used. Commencing with the July, 1927 admissions of moderately advanced cases, 100 of such consecutive admissions were removed. From these moderately advanced cases, those receiving collapse were segregated, being 9 in all. Therefore, to get parallel admissions as to time span, every tenth noncollapse case was selected for the random sample to be used for comparative purposes against the 9 collapse cases. The next 100 successive admissions were segregated and sampled the same way. This was done until the 821 cases were so treated. Such a sampling procedure is necessary to correct for the fact that during the early dates shown in this study a very small proportion of cases received collapse while toward the end of the admission study over one-third were receiving collapse. By such a method the question of bias in favor of time or period is avoided. If the time element were not considered one might justly raise the question of one group receiving different attendant care than the other because the majority of the collapse cases accrued

in the final years of this case survey. Changing sanatorium policies, if any, are likewise accounted for because to have divided 821 by 201 and taken every fourth case for the random sample, would have been to disregard the time element.

Though moderately advanced cases as such make relatively homogeneous statistical material, they must be comparable as to race, sex and age. All of the subjects in this study were white. Table 2 shows the age and sex distribution. There appears to be a slight tendency to select younger age groups for collapse. The median age of the collapse group is twenty-six years and ten months, while that of the noncollapse is

TABLE 2

Moderately advanced cases by age and sex: collapse and noncollapse groups

AGES	COLLAPSE			NONCOLLAPSE		
	M	F	Total	M	F	Total
years						
17–20	13	19	30	10	9	19
21–25	31	31	62	29	28	57
26–30	35	26	59	33	30	60
31–35	10	17	31	14	17	32
36–45	10	5	15	15	8	25
46+	3	1	4	6	2	8
Totals.....	102	99	201	107	94	201

exactly twenty-eight years. The selection difference here is only fourteen months. For practical purposes the sex and age distribution in the collapse and noncollapse group is comparable.

METHOD OF STUDY

Morbidity and mortality comprise the standards of comparison. The latter is admittedly weak because in both groups it is too small to give usable age-specific or annual rates, but table 3 reveals a significant difference between the crude death rates of collapse and noncollapse cases. When considering this point it must be constantly borne in mind that patients at Trudeau are studied for an actual need of collapse therapy before it is instituted. A case usually is collapsed only after a reasonable trial and observation on rest alone. At first one is disinclined to secure much encouragement from collapse statistics obtained under such conditions. However, he needs only to turn to the problem of diabetes to

find a corollary. Diabetics requiring insulin as well as diet regulation have a higher diabetic death rate than do those controlled by diet alone. This does not detract from the value of insulin nor does it destroy the opportunity to appraise the value of insulin.

In an attempt to find some obvious way to demonstrate that the collapse cases are basically less resistant than those not so selected, length of stay in the sanatorium was chosen for an index. There may be factors, other than case selection, that keeps the collapse case in the sana-

TABLE 3

Deaths, tuberculous and nontuberculous, while in the sanatorium and for five subsequent years

POST-ADMISSION TIME PERIOD	COLLAPSE GROUP		NONCOLLAPSE GROUP	
	Deaths—tuberculous	Deaths—other	Deaths—tuberculous	Deaths—other
In sanatorium	4	—	1	—
1st post-sanatorium year	2	1	—	2
2nd post-sanatorium year	5	—	1	—
3rd post-sanatorium year	3	1	—	1
4th post-sanatorium year	3	1	—	—
5th post-sanatorium year	4	1	2	—
Totals	21*	4	4*	3

* Ratio collapse tuberculous deaths to noncollapse = 5.25:1.

TABLE 4

Patient-months spent in sanatorium prior to discharge of first admission

GROUP	TOTAL	AVERAGE
Collapse	2,046.5	10.18
Noncollapse	1,351.5	6.72
Excess-collapse	695.0	3.46

torium longer than the noncollapse case, but the findings of this study are contrary to the popular belief that collapse will shorten the patient's stay in a sanatorium. From table 4 it is obvious that the increase of sanatorium care by 3.46 months, or 66 per cent, given to the collapse cases over noncollapse cases is a significant difference. One frequently thinks of the collapse case as the ambulatory patient probably needing the least sanatorium supervision. Granted that moderately advanced collapse cases are selected risk cases, it is evident at this point that their collapse has not reduced their sanatorium stay to equal that of the noncollapse

cases. Neither has this therapeutic agent reduced this group's death rate to any figure comparable to their more resistant cohorts.

Further study is directed toward morbidity as based upon a five-year follow-up of each patient. Table 5 shows the remarkably small number of cases lost sight of during the follow-up years. Many of these five-year follow-up studies have just ended bringing this study up to date as much as possible. There are admitted weaknesses in the follow-up system used at Trudeau. The most important weakness is that personal communications by mail are used in many instances and such is not always trustworthy. But table 5 indicates that the spirit of patient cooperation must be excellent. This notwithstanding, it would seem that

TABLE 5

Deficiencies in follow-up: Number lost prior to completion of five-year post-sanatorium period, by years

POST-SANATORIUM YEARS	COLLAPSE GROUP	NONCOLLAPSE GROUP
1st	—	1
2nd	—	4
3rd	—	—
4th	—	1
5th	—	—
Totals.....	0	6*

* None of these cases had relapsed prior to losing them. All relapsed cases were followed five years or to death.

the tendency for error would be the same in either group. The hypersensitive individual may report an untrue relapse, but this will be somewhat neutralized by the phlegmatic personality who reports that all is well when he has actually lost ground. However, these two disturbances should affect the collapse and noncollapse groups equally and in the aggregate, by rule of chance, that which hurts the statistics of one group should equally damage those of the other.

When relapsed years are counted by summation for each group for each year, and for the five years, it is seen in table 6 that, as might be expected, the morbidity in the collapse group is higher than in the other. Whereas the mortality rate is 5.25 to one in favor of the noncollapse, the morbidity is only 1.64 to one. (Does this indicate the questionable value of trying to calculate morbidity loads in general from mortality rates?)

That to-day, like many other institutions, Trudeau is putting nearly

all of the less favorable risk cases into the collapse group has been admitted. This being true, we should notice to-day that those remaining in the noncollapse group are a highly selected favorable group with recovery rates much better than the noncollapse group of a few years ago when only a few of their less favorable cohorts were placed in the category of collapse. For inquiry into this question, 200 consecutive noncollapse

TABLE 6

Post-sanatorium patient-years of relapse after discharge—total and by years

POST-SANATORIUM YEARS	COLLAPSE GROUP	NONCOLLAPSE GROUP
1st	28	19
2nd	25	17
3rd	17	8
4th	14	11
5th	21	9
Total years.....	105	64

TABLE 7

200 consecutive moderately advanced cases treated without collapse from July, 1927 to May, 1929, and 200 from October, 1930 to October, 1933, showing mortality and morbidity for five years after patients' discharge

POST-SANATORIUM YEARS	PATIENT-YEARS OF RELAPSE		DEATHS—TUBERCULOUS		DEATHS—NONTUBERCULOUS	
	1927–1929	1930–1933	1927–1929	1930–1933	1927–1929	1930–1933
1st	24	14	2	2	1	2
2nd	26	12	3	2	—	2
3rd	20	4	1	—	1	2
4th	22	15	2	2	—	1
5th	18	7	1	3	—	1
Total.....	110	52	9	9	2	8

Note that it required twenty-two months to accumulate the earlier 200 cases and thirty-six months for the later when more collapse was used.

cases were selected at a time when less than one in ten new admissions were collapsed, and for comparison 200 such cases were selected when more than one in three were so treated. The latter noncollapse group should prove to be a better risk group than the former because theoretically most of the less favorable cases are in the collapse group at this later time period, whereas in the earlier period a considerable number of poor risk cases must have been denied collapse measures. Table 7

indicates that this appears to be a correct conclusion so far as morbidity is concerned, but it is to be noted that the death rate is the same during both time periods. However, to draw conclusions from small numbers leads to the pitfalls of chance play. (There is no obvious reason, other than chance, why one group should have a nontuberculous death rate four times as great as the other.) On the other hand, the figures in the morbidity columns are large enough to permit a guarded conclusion that we do have evidence to-day that we are placing more and more of our less favorable risk cases under collapse therapy. Given twice this number of cases for study and with the same resultant ratios, we could make a positive conclusion to this effect.

TABLE 8

200 moderately advanced cases, including collapse cases, by consecutive order of admission from July, 1927 to April, 1929, and 200 from July, 1931 to October, 1933, showing mortality and morbidity five years after discharge

POST-SANATORIUM YEARS	PATIENT-YEARS OF RELAPSE		DEATHS—TUBERCULOUS		DEATHS—NONTUBERCULOUS	
	1927–1929	1931–1933	1927–1929	1931–1933	1927–1929	1931–1933
1st	33	22	2	3	1	2
2nd	31	15	3	5	—	1
3rd	18	9	1	2	2	2
4th	20	14	2	3	—	1
5th	16	9	2	3	—	1
Totals.....	118	69	10	16	3	7

Further inquiry is based upon the hypothesis that collapse therapy has no virtue nor harm in moderately advanced cases. If this is true, then 200 consecutive new admissions in the time period when collapse was little utilized should have the same morbidity rates as later when over one-third of the cases were collapsed. (We must admit any slight general trend tendency during the total time interval as an exception to this statement.) From table 8 such an hypothesis would appear to be open to question because the morbidity seems to be lowered in post-sanatorium moderately advanced tuberculosis when collapse is more liberally utilized in this group as a whole. During the total time period used in this study all post-sanatorium morbidity has been lowered by 2 per cent which is a general trend that can hardly account for the 42 per cent drop noted in table 8. Here again, in spite of the fact that the figures used here are the largest we can accrue from Trudeau's records,

the total case experience is small and positive conclusions must be supplanted by suggestive findings. Evidence that morbidity is actually reduced is further supported by combining the morbidity findings of table 7 with table 8. Certainly no viewpoints can be substantiated by the mortality findings.

DISCUSSION

The findings of this study would seem to indicate that the true and final evaluation of collapse therapy, as to its effect in curing tuberculosis, is yet to be made. Further, it is indicated that though collapse therapy when used in moderately advanced cases may be productive of superior results in the management of isolated cases, it has not made itself strongly felt in changing the end results of the group as a whole.

Those patients at Trudeau who did not receive collapse therapy showed much better morbidity and mortality rates than those who did. Unless one wishes to state that collapse does harm rather than good, this indicates that cases subjected to collapse procedures were properly selected. They were selected according to indications of a need for such therapy. This is proper therapeutics for any disease. However, the important discovery of this study was the finding that collapse, when indicated, was not of enough value to the individual to make up for what he did not possess in intrinsic resistance. In other words, in this study of moderately advanced cases, collapse therapy has not proved to be a substitute for an individual's acquired or inherent immunity or resistance. Should it have been found by these actuarial methods that those cases showing a need for collapse therapy had end results even as good as those not needing it, then we could unequivocally state that this therapeutic agent is a potent force in the cure of tuberculosis. Unfortunately this was not found to be the case. This may not surprise some physicians. To all, however, it challenges the right to advocate wholesale utilization of collapse therapy on a mass production basis. It would seem that further studies of this nature might well be repeated and, if these findings can be reasonably confirmed, they should be used to modify the popular demand, both in and out of the medical profession, for more and more collapse facilities. Perhaps those "neglected" patients forced to remain in bed because collapse therapy is not available to them are not, in many instances, neglected at all. This is a rude statement to make about such a popular subject as collapse therapy. Such a statement is sincerely appreciated by the writer as his own findings proved to be a bitter pill to

swallow because more optimistic results were expected when the study was begun.

Though it is difficult to prove, it is believed that this study does show that to a limited extent collapse measures are effective. Undoubtedly, without these measures, the end results seen to-day for the tuberculosis cases as a group would be less favorable than they are (tables 7 and 8). But unless the end results of collapse cases can be shown to be as good as the noncollapse cases when careful selection is made, the force of this therapeutic procedure can only be estimated rather than measured. Perhaps what is most needed to-day is a new appraisal of the specific indications for collapse measures already at hand rather than a constant search for new techniques.

SUMMARY

A comparison is made of five-year end results in 201 consecutive cases of moderately advanced tuberculosis treated with, and 201 treated without collapse therapy at Trudeau Sanatorium. Direct and indirect methods of analysis were employed in an attempt to show the effect or force of collapse on the end results of such cases. No improvement was noted in mortality when collapse was used. Improvement in the five-year morbidity study was noted for the cases as a group when collapse was more liberally used, but positive conclusions to this effect cannot be made for all moderately advanced cases because of the limited number of cases for study.

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JACOBAEUS OPERATION[1]

A Plea for Its Early Use in the Treatment of Incomplete Collapse

SAMUEL ALCOTT THOMPSON[2] AND MORTIMER GREENBERG[3]

Collapse therapy, properly applied, offers the majority of tuberculous patients the possibility of becoming well. In this day of collapse therapy it is no uncommon thing to see X-ray films of patients receiving intensive pneumothorax therapy, in whom the collapse is most effective in the healthy part of the lung, while the diseased part remains uncollapsed (figure 1). For one to say, "Collapse therapy should collapse the diseased part," would seem ridiculous, but for one to "produce collapse that does not collapse the diseased part," would seem to be an everyday occurrence.

Incomplete collapse may produce a marked clinical improvement for a time, yet most of these patients will eventually die of their tuberculosis.

The standard of successful collapse therapy is universally accepted as being the closure of the cavity and the disappearance of the tubercle bacillus from the sputum. When one method is unsuccessful it should be abandoned and replaced by another. Sometimes, a series of methods is applied, one after the other, before successful collapse results.

Alexander has recently written, "I have occasionally reviewed the histories and roentgenograms of patients whose disease has advanced to a hopeless state, or who have died, and I have been impressed by the fact that at one time in the course of their disease, many of them presented ideal indications for some operation, often a minor one, and that many of them might have been saved if surgery had been used at the opportune time." If this be true, why then do we not employ the smallest operation that can offer a reasonable chance of complete collapse, early in the disease when the indication arises?

I believe the answer to the above question lies in the lack of recognition as to what constitutes "ideal indications" and "the opportune time." For the Jacobaeus operation, the ideal indications are necessarily the

[1] Read before the New York Tuberculosis and Health Association at the New York Hospital, New York City, December, 1940.

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[3] Hillside, New Jersey.

presence of restraining adhesions, and the opportune time is as early after the initial pneumothorax as possible, which is a matter of weeks rather than months.

Efficient pneumothorax indicates a selective collapse, in which the diseased part is collapsed and the healthy part is expanded, or relatively so. Inefficient pneumothorax gives rise to two groups of patients having definite indications for the Jacobaeus operation. (*1*) Patients in whom the cavities have not been closed because of restraining adhesions. (*2*) Patients whose sputum may be negative for the tubercle bacillus and in whom the cavities appear to be closed. However, they have sustained a collapse of the entire lung, including the healthy part, but it is necessary or desirable to secure a selective collapse because of a reduced vital capacity or a contemplated collapse of the contralateral lung. In the first group the indication is to produce sputum conversion, and in the second group the indication is to produce selective collapse. (Figure 3.)

The suitability of adhesions for division is determined primarily from a study of the X-ray films and fluoroscopic examination; however, the final decision can be made only after actual examination through the thoracoscope. Increasing experience has demonstrated the unreliability of X-ray studies to determine the suitability of adhesions for severing. (Figure 2.)

Whenever there is doubt as to the suitability of adhesions, we strongly urge that a thoracoscopy be performed. The safety of this procedure has been repeatedly demonstrated and it is occasionally possible to completely sever adhesions that seemed to be impossible or unsuitable from a study of the X-ray films. (Figure 2.) In the present group of patients,

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FIG. 1. This X-ray film illustrates an inefficient pneumothorax in which the healthy part of the lung is collapsed but the diseased area is uncollapsed because of restraining adhesions.

FIG. 1a. This is an X-ray film of the patient as illustrated in fig. 1, taken after a Jacobaeus operation. The lung was attached to the chest wall by a broad, thick adhesion.

FIG. 2. This X-ray film illustrates the impossibility of deciding by X-ray alone which adhesions are suitable for division. From a study of this X-ray film the adhesions seem unsuitable.

FIG. 2a. This is an X-ray film of the patient illustrated in fig. 2, after a Jacobaeus operation, showing how it is occasionally possible to free a lung that is extensively adherent.

FIG. 3. The disease in the upper right lung was considered to be under control. However, a Jacobaeus operation was suggested to further increase the selective collapse on the right side as a preliminary to some form of collapse therapy on the contralateral side.

FIG. 3a. This is the X-ray film of the patient illustrated in fig. 3, after a Jacobaeus operation. Notice the increase in the selective collapse on the right side.

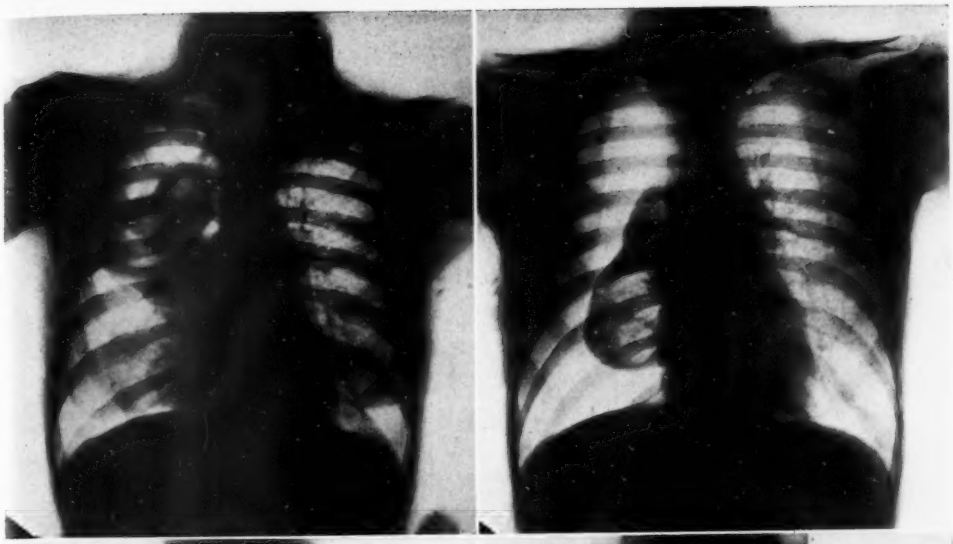

FIG. 1

FIG. 1a

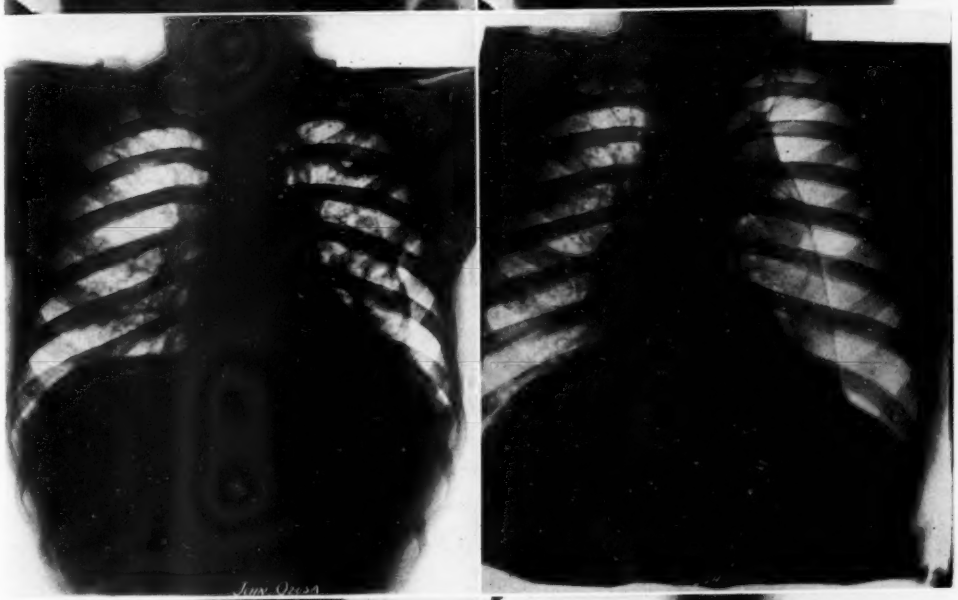

FIG. 2

FIG. 2a

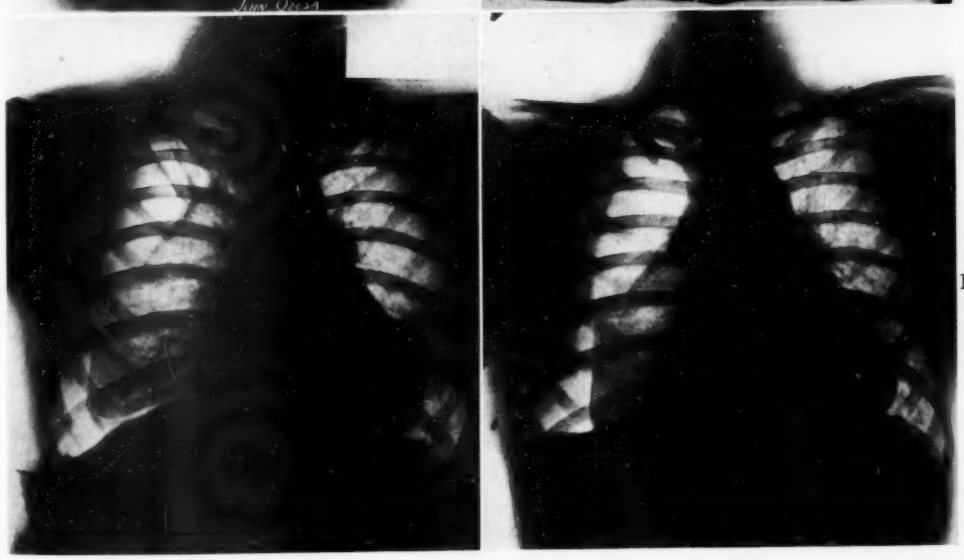

FIG. 3

FIG. 3a

FIGS. 1-3a

exploratory thoracoscopy was performed 21 times with no complications. We feel that this attitude towards exploratory thoracoscopy is conservative, as many times it has prevented the necessity for a more radical form of surgical collapse.

The opportune time to change from one form of collapse therapy to another is not always easy to determine, but experience and statistics show that this time is early rather than late, following pneumothorax induction.

It is well known that in a tuberculous lesion there occurs an early period of rapid lung retraction, followed by a period in which the lung retraction is slow. If the collapse is efficient during this early period of rapid lung retraction, a more complete healing and firmer scar results. If the collapse is inefficient and the process of retraction is hindered by restraining adhesions, healing occurs much more slowly or may never be complete. A shorter period of collapse therapy is necessary when the collapse takes place during the stage of rapid lung retraction. A cavity that requires a long time to become closed with pneumothorax will require a still longer time to become firmly healed, and much longer than the cavity that closed within a short time after the initial pneumothorax. These facts were shown in considerable detail by Barnwell in Alexander's recent book.

Bendove showed that the largest number of pneumothorax failures, due to "no free space," occurred in those patients who had a long duration of illness before the pneumothorax was attempted. Also, the shorter the duration of illness before the pneumothorax was instituted, the greater the chance of sputum conversion. Following the first month of pneumothorax therapy, there was a progressive decline in the number of sputum-converted cases.

At the time of the initial pneumothorax and for a short time thereafter, the pleura is in a virginal state—thin, glistening and translucent. At this time it is more resilient and more easily divided than at any other time. It is more easily stripped from the chest wall along the line of cleavage of the endothoracic fascia when it is thin than when it is thickened. The nearer the pleura approaches normal, the less the congestion and the smaller the number of blood vessels encountered.

At varying lengths of time after the initial pneumothorax, a large percentage of the cases are complicated by the formation of fluid in the pleural cavity. With the formation of this fluid, a decided change occurs in the pleura. There is no longer the glistening appearance, the trans-

lucency and thinness give way to a thickened, dull, gray-yellow pleura, many times covered with fibrin deposits. This thickened pleura may not only prevent the reëxpansion of the lung after the termination of the pneumothorax, but also prevent the establishment of a selective collapse, following a technically successful Jacobaeus operation.

When these changes have occurred in the pleura, the operator is at a decided disadvantage, both as to the performance of the operation, and the results obtained.

Because of the thickened pleura, the adhesions are firmer and thickened. Transillumination may be impossible. The inability to determine the presence in or relation of lung tissue to the adhesion, increases the number of cases in which the actual division of the adhesion is not attempted. In the broad thick adhesion, where it is necessary to decolate the peripheral attachment from the chest wall, the technical accomplishment of this is made easier by a thin pleura, free of congestion.

Contrary to the general belief, after an initial period of adjustment, adhesions instead of becoming stretched and thinned out, actually become thickened, especially when fluid is present. Microscopical examination of the adhesions shows the predominance of fibrous tissue over elastic tissue so that contraction rather than stretching takes place. The stretching and thinning that does occur is usually from the visceral side of the pleura, and continued attempts by pneumothorax to stretch these adhesions may result in a perforation of the lung at the site of the adhesion attachment.

It is usually possible to determine the presence or absence of adhesions soon after the initial pneumothorax. Careful study and repeated examinations in the first two or three weeks will reveal the effect of the adhesions upon the degree of collapse. If the adhesions are definitely restraining collapse of the diseased part at the end of three weeks, we believe that a Jacobaeus operation should be done at that time. If there is some collapse, and the cavity is smaller at the end of the three weeks, pneumothorax therapy should be continued for an additional three weeks. At the end of six weeks, if the pneumothorax is inefficient because of any restraining adhesions, an attempt should then be made to sever the adhesions.

The following statistics (tables 1, 2 and 3) were gathered from two sources. All of the first group were patients in the Municipal Sanatorium at Otisville, New York. The second group of patients were operated upon in four different hospitals in New York City. In the first group

of 111 patients there were 125 operations of which 21 were exploratory thoracoscopies and 104 were Jacobaeus operations. There were 14 patients who had two Jacobaeus operations. No patients in this group

TABLE 1

Results of Jacobaeus operation

	GROUP I	GROUP II
Positive before operation	70 (76.1%)	39 (100%)
Negative before operation	*22 (23.9%)	0
Patients who could not be followed	5 (5.4%)	0
Sputum conversion after operation	50 (76.9%)	35 (89.7%)

* Operated upon to produce a selective collapse which occurred in every case to varying degrees.

TABLE 2

Complications

	GROUP I	GROUP II
Clear fluid, negative for tubercle bacilli	4	2
Tuberculous empyema, positive for tubercle bacilli:		
Clear fluid	3	1
Cloudy fluid	3	0
Mixed infection empyema	0	0
Haemorrhage from adhesions	2	1
Haemorrhage from intercostal artery (died)	1	0
Subcutaneous emphysema	13	3

TABLE 3

Percentage of patients coming to surgery in group I

Total admissions (April 1, 1939 to October 31, 1940)	1,052
Patients treated with artificial pneumothorax	457 (43.4%)
Patients receiving Jacobaeus operation	92 (20.1%)
Patients receiving exploratory thoracoscopy	19 (4.1%)
Patients coming to surgery	111 (24.2%)

required more than two Jacobaeus operations. In the second group of 39 patients there were no exploratory thoracoscopies and all Jacobaeus operations were completed at the first operation.

Many of the patients in the first group came under our observation after pneumothorax had been started in other institutions, therefore we

did not have the opportunity of observing them early in the course of pneumothorax therapy. The average length of time between the initial pneumothorax and the Jacobaeus operation was six months in this group.

The patients in the second group came under our observation soon after the initial pneumothorax had been performed. The average length of time between the initial pneumothorax and the Jacobaeus operation was five weeks.

The successful results, with sputum and gastric contents negative for the tubercle bacillus, were 76.9 per cent in group I. This figure compares favorably with most of the published results up to date, but does not compare so favorably with the corresponding figure in group II, in which successful results were obtained in 89.7 per cent of the patients. We attribute the better results in group II to the early Jacobaeus operation.

The complications in group I were 25 per cent, and in group II 18 per cent. In both groups subcutaneous emphysema was the most frequent single complication, it was also the most unimportant complication and in no instance was the pneumothorax lost.

The mortality in group I was 1.0 per cent. One patient died from haemorrhage which was apparently due to perforation of an intercostal artery on inserting the trocar. There was no mortality in group II.

CONCLUSIONS

The Jacobaeus operation is a conservative procedure because it will frequently obviate the necessity for a later and more radical method of surgical collapse. In patients with inefficient pneumothorax due to adhesions, we feel that the opportune time for the Jacobaeus operation is from three to six weeks after the initial pneumothorax, for the following reasons:

1. The pleura is more nearly normal and, for this reason, technical difficulties are reduced.
2. The completion of collapse can take place during the stage of rapid lung retraction and selective collapse is more apt to occur.
3. The period of pneumothorax is shortened because of the more complete collapse and closure of the cavity.
4. There is a larger percentage of successful results with sputum conversion when the operation is performed weeks rather than months after the initial pneumothorax.

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TUBERCLE BACILLI IN CAVITY DRAINAGE (MONALDI)[1,2]

EMIL BOGEN AND WILLIAM DUNN

The institution of suction drainage of tuberculous cavities (1), at the Olive View Sanatorium (2), made it possible to examine the contents of such cavities during the course of treatment. All of the aspirated material was concentrated and the number of tubercle bacilli present determined each day (3). Twenty-four hour sputum specimens from these patients were also examined, daily during the first week, weekly during the next six weeks, and monthly thereafter. Additional examinations, cultures, gastric lavage, etc. were done as requested.

A reduction in bacterial content of both sputum (table 1) and cavity drainage material (table 2), often leading to sputum conversion, occurs in many cases treated by the Monaldi technique. This apparently favorable change may even be observed in some cases in which the aspiration has no effect on the size of the cavity or its eventual fate, and may be followed, especially after removal of the drainage tube, by a reappearance of the organisms in the sputum.

The first effect of cavity drainage is the mechanical removal of any depot or store of bacilli present in the cavity, which would otherwise be expectorated later, without necessarily affecting the rate of production of such bacilli. However, the bacterial content of the material aspirated from the cavities was, in many instances, of the same magnitude as the previous daily bacillary excretion in the same cases. Most of these organisms would probably have been expectorated the next day, if they had not been aspirated. This suggests that, in these patients, there was not a great reservoir of bacilli, only a few of which were expelled each day, but that the output corresponded with the number of organisms being produced daily. The relative uniformity of the number of tubercle bacilli found in the sputum on successive days in many cavity cases points in the same direction.

Some of the tubercle bacilli in the sputum arise from softening, lique-

[1] From Olive View Sanatorium, Olive View, California.

[2] With the aid of Work Projects Administration, Project No. 665-07-3-223, Los Angeles County, California.

faction and excretion of the tissue containing the organisms (4). Such production occurs only as rapidly as tissue is actually being destroyed and, except in the case of continually progressive lesions, should be self-limited. Organisms multiplying in the tissues may also be carried out and excreted into the cavity contents by phagocytic cells or fluid exudate, "washing" them out of the tissue spaces. Such cleansing of the cavity

TABLE 1

Tubercle bacilli in sputum

AVERAGE DAILY NUMBER OF TUBERCLE BACILLI	TIME AFTER PUNCTURE					
	1st week	1 month	2 months	3 months	4 months	6 months
3,000,000	5	3	1	1	1	0
300,000	5	5	2	3	1	1
30,000	4	2	5	1	2	1
3,000	1	2	4	2	4	3
Negative	2	5	5	10	5	6
Died or discharged	0	0	0	1	4	6

TABLE 2

Tubercle bacilli in cavity drainage

AVERAGE DAILY NUMBER OF TUBERCLE BACILLI	TIME AFTER PUNCTURE					
	1st week	1 month	2 months	3 months	4 months	6 months
3,000,000	4	1	0	0	0	0
300,000	8	4	1	0	1	0
30,000	1	4	2	1	2	1
3,000	3	5	3	3	2	2
Negative	1	3	6	7	5	3
Discontinued	0	0	5	6	8	11

by drainage may occasionally be suggested by the large volume of drainage material obtained. Often, however, this was no greater than the volume of sputum previously obtained from these same patients. No such physiological lavage by aspiration of increased fluid exudate could then be assumed.

Additional tubercle bacilli may be expected to arise from the growth of the organisms in the culture material of the wall and contents of the cavity. These may be functionally independent of the living tissues,

except for warmth and occasional increasing food supply from disintegrating material in the cavity walls. The mechanical removal of the organisms, multiplying within the cavity lumen, may be expected to lessen bacterial production, by removing a large part of the media in which such multiplication occurs, as well as by lessening the number of organisms remaining to divide.

Changes in the cavitary physiology resulting from drainage may also reduce the multiplication of tubercle bacilli. Organisms lying free within the cavity lumen, in the disintegrating cellular material of the pyogenic membrane lining the cavity, in the intercellular spaces and in the phagocytic cells in the vicinity may multiply at variable rates, depending in part on the environmental situation. The temperature within the cavity is little affected by aspiration, but the lessening of moisture by the suction may be more apt to interfere with optimal bacterial growth (5).

Although the tubercle bacillus can withstand exposure to strong acids or alkalis for periods which would be fatal to other bacteria, marked changes in the pH of the medium in which it is growing may affect its rate of multiplication and perhaps also its virulence (6). The hydrogen ion concentration of cavity contents examined here was generally slightly acid, with a pH ranging from 4.5 to 7.4. The acidity of the cavity contents was considerably affected by the type of contaminating organisms present and often changed on further incubation. Direct smears, aerobic and anaerobic cultures of the cavity material showed nonhaemolytic gram-positive cocci to constitute the predominating nontuberculous flora. Gram-negative cocci and bacilli were also frequently present. Haemolytic streptococci, spirilla and fusiform bacilli and spore bearing anaerobes were rarely found in this series.

The cavity contents obtained through direct aspiration were generally found to be more acid than the sputum from the same patient. The acidity of the sputum is modified by admixture with saliva and buccal secretions, as well as by the products of the mouth organisms which may contaminate it. In general, the larger the volume of the sputum or cavity material, the more acid was its pH. Differences in the hydrogen ion concentration in the sputum or cavity contents of different patients, and at different times in the same patient (7), may be effects as well as causes of changes in the amounts and type of bacteria present.

The importance of the gaseous milieu for the growth of tubercle bacilli has been repeatedly emphasized. Suspended respiration of the tubercle

bacillus, in the absence or reduction of oxygen, has been cited as evidence of the strict aerobiosis of these organisms (8). Closure of a bronchus and the prevention of the passage of oxygen through it to a cavity should, therefore, inhibit the development of tubercle bacilli (9). This procedure has been tried both in animals and in man (10).

Early in the Monaldi treatment, air is aspirated in through the bronchi and out through the catheter. The oxygen content of the cavity air is then increased over that prior to the establishment of the drainage. Such increase in the oxygen content of the cavity by drainage is just the opposite of the condition, above advised, for inhibiting the growth of tubercle bacilli. Nevertheless, the progressive lessening of the number of tubercle bacilli accompanying prolonged cavity drainage is too marked and frequent to be ignored. Merely opening the abdomen and allowing free entrance of air has been reported to lead to subsidence of tuberculous peritonitis with effusion. The presence of air, instead of stimulating tubercle bacilli to increase proliferation, here also seems to exert the reverse effect, or stimulates the body tissues to increased defensive activity (11).

Prolonged cavity aspiration results in a radical change in the physiopathological conditions existing in and around tuberculous cavities. Study of the drainage material and the concomitant sputum has shown reduction or disappearance of tubercle bacilli in a large proportion of the cases so treated. Factors responsible for this result have been suggested although the entire mechanism is not yet clear. Irrespective of the immediate clinical value of direct suction drainage of tuberculous cavities, the procedure may yield considerable information regarding the physiology, pathology and bacteriology of the cavities treated.

SUMMARY

All of the material aspirated from 17 tuberculous cavities by the Monaldi method of transthoracic puncture and prolonged suction drainage was examined and compared with the sputum obtained from the same patients. Tubercle bacilli diminished or disappeared from these specimens in many cases. Physiological, pathological and bacteriological factors which may contribute to this result include mechanical removal of bacteria and other cavity contents, intercellular lavage by induced transudation, increase in the hydrogen-ion concentration and changes in the composition of the gaseous milieu.

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RELATION OF SEX TO THE COURSE OF EXPERIMENTAL TUBERCULOSIS IN MICE[1,2]

ESMOND R. LONG AND AGNES BEEBE VOGT

Sex, age and race are important factors in the mortality curves of human tuberculosis. In both sexes the tuberculosis death rate rises abruptly after adolescence. The rise is more rapid in young women than in young men. The facts suggest that sexual maturation is more important than age *per se*, and that the sexual factor has more influence in the female than male sex.

It has been argued that the sudden rise in seriousness of tuberculosis with the onset of adolescence is environmental rather than constitutional in origin, on the ground that a child's contacts are rapidly widened at this period of life. However, it seems unlikely that increased contact with tuberculosis leading to progressive primary disease or serious exogenous infection can be as abrupt as the rise that takes place in the incidence of fatal tuberculosis with the development of adolescence. There seems as good or better reason for associating the rise in tuberculosis with adolescence itself.

Man's environment is so variable that satisfactory evidence for either an environmental or constitutional explanation of the rise in tuberculosis with adolescence is unlikely to be obtained. In animals, on the other hand, environment can be made identical for constitutionally variable groups, so that the influence of constitution can be studied. It would appear therefore that resistance to tuberculosis, as modified by sex, can be studied most profitably in animals.

On the basis of this reasoning it was decided to carry out a series of experiments on adolescent animals in the normal sexual state, animals with the sex organs removed and animals treated with sex hormones. Orientation experiments suggested that mice would be suitable animals for the test. The genetic uniformity of readily available strains appeared

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

[2] This investigation was carried out as a Coöperative Study with the National Institute of Health of the United States Public Health Service.

to be an advantage, and the relative simplicity of mouse tuberculosis seemed to remove a number of variables, such as the development of allergy and infection-induced resistance which complicate tuberculosis in guinea pigs and rabbits. It must be admitted, however, that a sex effect might be linked with the latter phenomena, and it must also be confessed that animals might be genetically uniform as respects coat color and other qualites and still heterozygous as respects resistance to a specific disease (Lurie (1)). However, an experiment with well known strains of mice, known to be susceptible to tuberculosis, appeared to have more advantages than disadvantages, and accordingly was undertaken.

An additional experiment on the effects of the gonadotropic hormones of pregnancy was included in the investigation. There was no thought of carrying out an exhaustive experimental study of the much debated subject of the effect of pregnancy on tuberculosis. Previous investigators of the relation of sex and tuberculosis have included the anterior pituitary and other gonadotropic hormones in their studies, and it was a simple matter to organize an experiment of the same character in the investigation here reported.

Mice are susceptible to infection with human, bovine and avian type of tubercle bacilli (see Calmette, Boquet and Nègre (2) for early literature). A number of studies of mouse tuberculosis have been recorded recently. It will not be necessary to cite more than a few of these, as the results secured by different investigators are not significantly different. One of us (3) reported a study of tuberculosis in albino mice several years ago summarizing the chief characteristics of mouse tuberculosis, as observed in that study, in which human type tubercle bacilli were used. The results then obtained correspond well with the picture of mouse tuberculosis as observed in the present investigation in which bovine type bacilli were employed. The abstract of the previous study is here repeated in part:

Following injection with the relatively large dose of 1.0 mg., injected intraperitoneally in mice of 25 to 30 g. in weight, a period of generalization ensued in which tuberculosis waxed and waned in different organs in a fairly regular sequence. First lesions, other than superficial involvement of the peritoneum and the regional lymphoid tissue, occurred in the spleen... Maximal involvement of the liver closely followed that of the spleen... In the lungs well developed lesions first appeared thirty days after inoculation and thereafter increased in severity, seething with bacilli, up to about eighty days, and then diminished. The majority

of tuberculous lesions seen after that period showed considerable evidence of healing.

The healing process was best observed in the lungs. In the period of maximum involvement, consolidations up to 2 mm. in diameter were common. The alveoli in these regions were filled with large phagocytic cells often so packed with bacilli that the cytoplasm could not be distinguished. At a later period the areas were much as before in extent, but the bacilli had largely disappeared, the alveoli being filled with degenerated phagocytic cells with abundant vacuolated cytoplasm frequently containing brown pigment. Still later. . .the areas were smaller and the cells for the most part small, with little cytoplasm, except for a central zone in which the large vacuolated cells persisted, with or without bacilli. No appreciable necrosis of lung tissue occurred, and, in the latest period studied, formerly tuberculous regions were represented by small zones of small monocytes (lymphocytes?) and slightly thickened alveolar walls.

Gunn, Nungester and Hougen (4) compared the course of tuberculosis induced in white mice by human, bovine and avian type tubercle bacilli. They found only minor differences in the progress of tuberculosis from the three strains. Pagel (5) discovered no striking difference in human and bovine type bacillus infections in mice, but noted that the disease produced by the avian bacillus was less severe. In all three types of infection a typical tissue reaction occurred, characterized by conspicuous proliferation of foam cells. Pagel described a conversion of the infecting bacilli from basophile to eosinophile rods, a change, in his opinion, correlated with reduced viability of the bacteria. Although typical allergy to tuberculin is generally conceded to be absent in the mouse, Pagel noted a distinctly enhanced response in reinfection as compared with first infection.

Recently Thomas and Dessau (6) have described the cellular response of the mouse to various fractions of the tubercle bacillus, noting reactions to bacillary lipoids comparable to the response to actual infection. They reported also an age difference in the susceptibility of mice. A continuation of their experience by Gerstl and Thomas (7) indicated that mice infected when between twenty and fifty days old are more resistant than either new-born or adult mice.

Almost all investigators have agreed that mice are susceptible to artificially induced tuberculosis and that the disease produced is generalized and characterized by chronicity, with partial regression in late stages

and absence of typical tuberculin allergy. All recognize the characteristic lesion as one composed almost exclusively of large mononuclear cells, often filled with bacilli, with occasional degeneration of the inflammatory mass and infiltration of other leucocytes but without typical caseation.

The most conspicuous lesions occur in the lungs. In the study here reported they were composed of large mononuclear cells with a cytoplasm that was relatively small in the early stages, increased and epithelioid-like in later phases, large in amount, foamy and often teeming with bacilli in mid-stages and foamy or much reduced in amount in late stages. Very frequently in the lungs of animals in the series here reported huge concentrations of bacilli were encountered in lesions of abscess-like character in which polymorphonuclear leucocytes predominated. In such cases it was impossible to tell whether an excessive number of tubercle bacilli resulted in chemotaxis for these leucocytes, or secondary infection had occurred, attracting polymorphonuclear leucocytes and stimulating in some way the multiplication of tubercle bacilli.

Experiments on the effect of sex hormones on tuberculosis have not been numerous or consistent in result. The literature has been summarized recently by Steinbach and Klein (8) and Gray and Brack (9, 10). Steinbach and Klein reported that the gonadotropic hormones of pregnancy retarded the course of tuberculosis when injected into tuberculous rabbits and guinea pigs. With few exceptions animals treated with antuitrin-S and pregnant mare serum fared better than the untreated controls. Anterior pituitary extract and placental extract (emmenin) however were not efficacious against tuberculosis.

Pierre-Bourgeois, Boquet-Sesensky and Pierre-Bourgeois (11) reported that castration, both of male and female guinea pigs, enabled them to live longer than control guinea pigs infected with tubercle bacilli. Injection of estrogenic substance (folliculin) and gonadotropic hormone accelerated the course of tuberculosis in female animals, while the injection of male and gonadotropic hormones seemed to prolong the life of males.

In an experiment reported by Störtebecker (12) normal guinea pigs appeared to be more resistant to tuberculous infection than ovariectomized guinea pigs, but the number of animals used seems too small to warrant sure conclusions. Studies on the effect of estrogenic substance were indecisive because of collateral injurious effects of the preparation injected.

Gray and Brack (9) were unable to demonstrate any effect of estrogenic

substance (progynon B) on immunity to tuberculosis in the female guinea pig, nor could they find any clear-cut difference in the severity of tuberculosis in either ovariectomized or non-ovariectomized female guinea pigs receiving antuitrin-S. Their protocols suggest that ovariectomy alone in guinea pigs did not exert a favorable influence.

Numerous experiments have been carried out on the effect of pregnancy on resistance to infectious disease. Kemp (13) found that pregnancy decreased the severity of syphilis in rabbits. Injection of pregnancy urine into female rabbits, however, did not modify the course of syphilis favorably. In general, female rabbits resisted the spread of syphilis better than males. The course of tuberculous infection in rabbits did not appear to be modified by pregnancy in a series of 240 animals studied by Burke (14), regardless of whether the rabbits were infected with the bovine or the human type of tubercle bacillus.

Experiments on the effect of male sex hormones have been relatively infrequent. Thomas and Duran-Reynals (15) found that testicular extract added to a suspension of tubercle bacilli greatly increased the severity of skin tuberculosis in rabbits and guinea pigs, over that seen in controls infected without addition of testicular extract. The enhancing effect was attributed to the "spreading factor" previously described by Duran-Reynals. The parenteral administration of large quantities of testicular extract to infected guinea pigs did not increase the extent of visceral lesions. Carnes and Biskind (16) found no effect from the implantation of pellets containing testosterone on the course of tuberculosis in immature guinea pigs.

The general problem has recently been considered by Sprunt (17), who concluded that sex hormones modify tissues so that resistance to infection is changed. However, the reported results as regards tuberculosis are indecisive, if not directly contradictory, and further investigation seemed desirable.

Five experiments were carried out in the investigation here reported. These are described separately in the following pages. All of them were organized for comparison of the resistance of normal animals and animals subjected to removal of sex organs or administration of sex hormones in large quantity.

Each mouse, as death from any cause occurred, was necropsied and gross and microscopical examinations were made of the viscera, with special attention to the lungs, spleen, liver and kidneys. In all cases

one series of sections was stained with hematoxylin and eosin and another with fuchsin and hematoxylin for the demonstration of acid-fast bacilli. For purposes of comparison the extent of tuberculosis in each organ was estimated roughly on the basis of both gross and microscopical examination on an arbitrary scale from one to four plus, the latter term indicating an involvement of three-quarters or more of the organ concerned. Sufficient variation in severity was apparent to make gradation between each integer desirable, and accordingly estimates of 0.5, 1.5, 2.5 and 3.5 plus were made (see tables 1 to 6). Figures 1 to 7 illustrate the typical course of mouse tuberculosis. Figures 1 to 4 show the sequence of pulmonary involvement in ovariectomized black mice, which was somewhat less severe in its course than that in normal and ovariectomized animals treated with theelin. Figures 5 to 7 illustrate the disease at its height in the lung, spleen, liver and kidney in unoperated, untreated animals.

EXPERIMENT 1

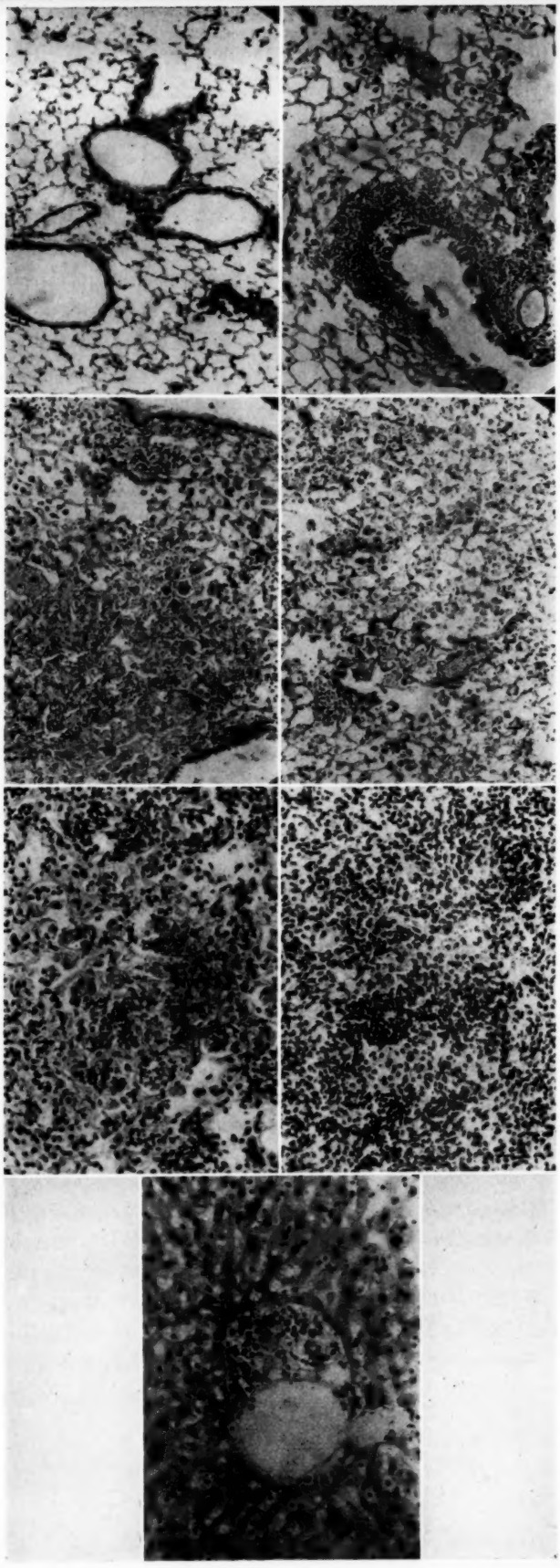
FEMALE BLACK MICE

NORMAL, OVARIECTOMIZED AND OVARIECTOMIZED WITH SUBSEQUENT TREATMENT WITH ESTROGENIC SUBSTANCE

One hundred and forty-nine mice of the Bar Harbor C 57 strain were used in this experiment, divided approximately equally in the three groups noted in the heading above. They were from 18 to 27 g. in weight.

Serial tests by the vaginal smear method were made daily on a large group of ovariectomized mice to determine loss of estrus cycle. Only mice with typical smears, that is, predominance of leucocytes, without cornified epithelial cells, were used in the experiment. The allocation of animals finally followed for the duration of the study was as follows: normal, 51; ovariectomized and not treated, 52; ovariectomized and treated with estrogenic substance, 46.

The ovariectomized mice had their ovaries removed within a two-month period ending one month before infection. A bilateral lumbar incision was made in all of the normal mice to serve as a control measure on the possible effect of the operative injury alone. All of the mice were infected intraperitoneally on February 8, 1937 with 0.01 mg. of the Ravenel strain of bovine type tubercle bacilli, a strain of high virulence for rabbits and guinea pigs, long in use in this laboratory. Estrogenic substance in aqueous solution (theelin from Parke, Davis and Company) was injected subcutaneously each day except Sunday throughout the experiment in the group receiving estrogenic substance, beginning on the day of infection. The estrogenic substance



FIGS. 1–7

was injected in a volume of 0.1 cc. containing approximately one rat unit. Repeated observation had demonstrated its effectiveness in restoring the vaginal smear typical of estrus. On necropsy, the uterine horns of the group treated with theelin were noticeably larger than in the other groups.

Sets of animals from the three series were killed for comparison at 62, 107, 171 and 269 days after infection. With the exception of 11 that died at scattered intervals during the first three and a half months and the several series killed for observation all lived for five months or more.

In certain respects the course of tuberculosis was similar in all groups. However, quantitative differences that may be of significance were observed. Tables 1, 2 and 3 summarize the record of all animals in the experiment. A condensed general record of the results in each group is given in the following paragraphs.

Normal Females

Fifty-one mice were studied. The average length of life of the mice not killed was 235 days. A single unmistakable cause of death, other than sacrifice, was rarely evident. All animals had extensive tuberculosis. In addition, most of them suffered also from intercurrent progressive infections, chiefly bronchitis and small bronchopneumonic lesions. A few had amyloidosis of the spleen.

FIG. 1. Upper left. Lung of mouse 17 (ovariectomized), dying 63 days after intraperitoneal injection of 0.01 mg. of bovine type tubercle bacilli. The lung is normal except for early migration of mononuclear leucocytes from the walls of the bronchioles and blood vessels.

FIG. 2. Upper right. Lung of mouse 114 (ovariectomized), dying 114 days after infection. The migration of mononuclear leucocytes is more conspicuous than in fig. 1. The cells close to the bronchiolar wall are small, with little cytoplasm. Those more remote have become macrophages with abundant cytoplasm.

FIG. 3. Middle left. Lung of mouse 58 (ovariectomized), dying 258 days after infection. The lung is almost consolidated with macrophages with a large volume of cytoplasm.

FIG. 4. Middle right. Lung of mouse 77 (ovariectomized), dying at 349 days. The lesion has regressed, with clearing of many alveoli, but persistence of a number of vacuolated macrophages.

FIG. 5. Lower left. Lung of mouse 141 (normal), dying 239 days after infection. The lung in the region shown is consolidated. In the centre the cells are degenerated and polymorphonuclear leucocytes are present in the infiltration. Tubercle bacilli are numerous in the macrophages in the central zone.

FIG. 6. Lower right. Spleen of mouse 145 (normal), dying 243 days after infection. A few epithelioid tubercles are present in the central region, and many of the epithelioid cells contain tubercle bacilli.

FIG. 7. Bottom. Liver of mouse 158 (normal), dying 177 days after infection. There is a periportal concentration of mononuclear leucocytes, including young small cells and macrophages.

TABLE 1

Normal female mice (C 57 black) infected with 0.01 mg. bovine type tubercle bacilli—2/8/37

NUMBER	DATE OF DEATH	DAYS OF LIFE	DEGREE OF INVOLVEMENT			
			Lung	Spleen	Liver	Kidney
173	4/12/37*	62	2	2	1.5	0.5
174	4/12*	62	1.5	2	1	0.5
175	4/12*	62	0	2.5	1	0.5
176	4/12*	62	0	2	1	0
177	4/12*	62	0	2	0	0
183	4/12*	62	1	1.5	0	0
184	4/12*	62	0	1	0	0.5
168	5/26*	107	1.5	2.5	2.5	1
169	5/26*	107	3	3	1.5	0.5
170	5/26*	107	2	4	1	0.5
171	5/26*	107	1.5	2.5	1	0.5
172	5/26*	107	2	2.5	1	0.5
130	7/ 2	143	3	3	1.5	0
131	7/15	156	4	1.5	1	1
132	7/26	167	3.5	3	2	0
133	7/29*	171	2.5	2	2	0
137	7/29*	171	1.5	2	1.5	0.5
144	7/29*	171	2	2.5	1.5	0.5
150	7/29*	171	3	1.5	2.5	2.5
157	7/29*	171	3	2	2	1
151	8/ 2	174	4	—	—	—
162	8/ 2	174	4	2	—	—
158	8/ 5	177	3	2	2	0.5
163	8/11	183	4	2.5	1.5	1.5
134	8/19	191	2	—	—	—
135	8/25	197	1	2	1	1
136	9/ 3	206	4	3	1	0
139	9/ 5	208	3.5	2	1	1
152	9/25	228	2.5	2	0.5	1
164	9/29	232	3.5	2	1	1
178	9/29	232	3	2.5	2	1.5
140	10/ 1	234	4	2	1	1
141	10/ 6	239	4	3	2	0.5
153	10/ 9	242	4	2.5	0	0.5
145	10/10	243	3.5	3	2.5	0.5
146	10/16	249	2.5	2.5	3	1
165	10/16	249	3	2	0.5	0.5
154	10/18	251	3	2	0	—
142	11/ 5*	269	2	2	2	0.5
147	11/ 5*	269	3.5	3	3	0.5
148	11/ 5*	269	2.5	2.5	3	1
155	11/ 5*	269	3	2.5	2	1
166	11/ 9	273	2.5	2	1.5	1
167	11/ 9	273	4	3.5	2	1
149	11/20	284	2.5	2	3	1.5
179	11/22	286	4	2	1.5	2
180	11/28	292	2.5	1.5	0.5	0
159	12/ 3	298	1	2	1.5	0
181	12/ 5	300	1	2	0	0
182	12/ 5	300	3	2	1	0
160	2/ 1/38	358	2	2	2	0.5

* Killed.

TABLE 2

Ovariectomized female mice (C 57 black) infected with 0.01 mg. bovine type tubercle bacilli—2/8/37

NUMBER	DATE OF DEATH	DAYS OF LIFE	DEGREE OF INVOLVEMENT			
			Lung	Spleen	Liver	Kidney
22	3/12/37	32	0.5	3	2	0
19	4/12*	62	1	1	1	0.5
20	4/12*	62	2	1.5	2	1
21	4/12	62	0	1	1	0.5
37	4/12*	62	1	0.5	1	0.5
17	4/12	62	0.5	2	1	0
18	4/12*	62	1	2.5	1.5	0
23	5/26*	107	2.5	1.5	0	0
33	5/26*	107	1.5	1.5	1	0
34	5/26*	107	3	1	0	0
35	5/26*	107	2	0.5	1	0.5
36	5/26*	107	1	1	1	0
114	6/13	124	2	1.5	0.5	0
62	6/15	126	2	2	2	0
24	7/ 5	147	2.5	2	2	0
63	7/ 8	150	3	2.5	1.5	0
25	7/12	154	2	2	0.5	0
65	7/29*	171	3	—	1.5	1.5
126	7/29*	171	2	1.5	1	0.5
127	7/29*	171	1	2	1	1
128	7/29*	171	2.5	2	1	0.5
129	7/29*	171	2.5	2.5	2	0.5
54	8/ 1	173	4	2	0.5	0
115	8/13	185	4	2.5	0.5	0.5
46	8/19	191	3	3	—	—
55	8/19	191	3	2	1.5	0.5
50	8/20	192	2.5	2	1	0
51	9/ 9	212	3	3	0	0
72	9/20	223	3	3	2	0
116	9/25	228	3.5	2	2	1
117	9/28	231	1.5	2.5	0.5	0
96	10/ 5	238	3	3	0.5	0
102	10/23	256	1	2	1	0
58	10/25	258	3	—	0.5	0
73	10/30	263	2.5	2	1	0
118	10/31	264	2	1.5	1	0
119	11/ 5*	269	2	—	2	1
60	11/ 5*	269	2.5	2.5	0.5	0
74	11/ 5*	269	3	2.5	2	0.5
97	11/ 9	273	2.5	2.5	0.5	0
103	11/10	274	1	2	2	0.5
98	11/15	279	2	2	0.5	0
104	11/18	282	0.5	2	0	0
105	11/22	286	1	2	0	1.5
106	11/24	288	2.5	3	1	1
99	12/ 1	296	2	2	0	0
107	12/12	307	2.5	2	1	1
100	12/13	308	1	2	1	0
75	12/31	326	2	2	0	0
76	1/ 6/38	333	1	1	0	0
101	1/16	343	1	1	0	0
77	1/22	349	0.5	1	0.5	0

* Killed.

TABLE 3

Ovariectomized female mice (C 57 black) treated with estrogenic substance, infected with 0.01 mg. bovine type tubercle bacilli—2/8/37

NUMBER	DATE OF DEATH	DAYS OF LIFE	DEGREE OF INVOLVEMENT			
			Lung	Spleen	Liver	Kidney
39	2/23/37	15	0	2	2	0
109	4/12*	62	2	1	2	0.5
110	4/12*	62	0	0.5	2	0.5
111	4/12*	62	1	0.5	1	1
112	4/12*	62	1	0.5	1	0.5
113	4/12*	62	1	1	—	0.5
40	5/ 7	88	2	3	1.5	0
45	5/12	93	3	3	1	0
14	5/26*	107	2	2	2	0
16	5/26*	107	2	2	1	0
120	5/26*	107	3	2	0.5	0
42	5/26*	107	3	1	1	0.5
43	5/26*	107	2	1	1	0.5
44	5/26*	107	2.5	1.5	1.5	1.5
84	7/10	152	4	—	—	—
79	7/12	154	2	—	—	—
47	7/16	158	2.5	2	1	1
85	7/22	164	3	2.5	2	0
121	7/22	164	3	2.5	2	0
122	7/24	166	4	3	2.5	0.5
48	7/26	168	2.5	3	2	0
29	7/29*	171	1	1.5	1	0.5
49	7/29*	171	3	2.5	1	0
123	7/29*	171	3	2	2	1
124	7/29*	171	4	2	1	0
91	8/ 6	178	2	2.5	2	1
93	8/ 8	180	4	2	1	0
92	8/ 9	181	2.5	2.5	1	0.5
94	8/19	190	3	2	2	1
66	8/22	193	4	2.5	2.5	0
86	9/ 5	208	4	—	—	—
95	9/20	223	3	2.5	2.5	1
87	9/25	229	2	3	2	0
88	9/25	229	4	2.5	1.5	0
67	9/28	232	3	3	2.5	0
83	10/ 3	236	4	3	1	0
89	10/ 4	237	3	3	2	0
68	10/15	248	2.5	2	0.5	0
78	10/18	251	3	3	0.5	0
69	10/25	258	2	2.5	1.5	0
70	10/26	259	2.5	3	1.5	0
30	11/ 3	267	2.5	3	1	0
31	11/ 5*	269	2.5	2	2	0.5
32	11/ 5*	269	2.5	2	2	0
71	11/ 5*	269	1	2	1.5	0.5
108	11/ 5*	269	3	2	1	0.5

* Killed.

Lungs: A fairly well defined plateau of maximum involvement was evident, extending from the time of the first spontaneous death at 143 days to about the 286th day, by which time 46 of the original 51 mice were dead. In most of the mice surviving more than 250 days the tuberculous involvement tended to be regressive at the time of death. Three mice lived up to 300 days or more after infection, the last dying on the 358th day. Acid-fast bacilli were at all times numerous. The reader is referred to the opening section of this paper for a general description of lesions during the periods of maximum and regressing involvement.

As a matter of additional, although probably unrelated interest, it may be mentioned that squamous cell hyperplasias approaching, if not actually of neoplastic character were observed in 14 mice, or 14.5 per cent of the total number. Seven were found in the unoperated group (that is, normal before infection), 5 in ovariectomized and 2 in the animals ovariectomized and treated with estrogenic substance. There was thus no evidence of relation to the presence of the ovaries. The 2 animals receiving estrogenic substance died at an earlier age (average 208 days) than either the ovariectomized mice without this substance (average 298 days) or the normals (300 days).

Spleen: The extent of tuberculosis was variable throughout the entire period of observation, but the disease was always conspicuous. The organ was constantly grossly enlarged. As seen microscopically there was diffuse hyperplasia of the pulp and scattered throughout the pulp were small aggregations of epithelioid cells containing acid-fast bacilli.

Liver: As in the spleen the involvement was irregular in extent, being evident to some degree through the entire experiment. It was preponderantly periportal, although occasionally minute collections of mononuclear leucocytes were visible in the interior of the liver lobules. Acid-fast bacilli were present, but in much smaller numbers than in the spleen.

Kidneys: These organs were almost spared by the tuberculous process. Minute lesions, consisting of small mononuclear leucocytes and devoid of acid-fast bacilli, were present, being most conspicuous between the 180th and 280th day.

Ovariectomized Mice

Fifty-two animals were studied. The average length of life exclusive of animals dying in less than two months, and those sacrificed for observation, was 243 days. All animals in the series had more or less extensive tuberculosis, but certain differences from that seen in the normal

females were apparent, as will be shown in the following summaries for the different organs.

Lungs: A plateau of maximum involvement was evident, as in the case of the normal females. The early course of the disease, as seen in animals dead before the fifth month, showed that the extent of tuberculous invasion was on the upgrade from the first to the fifth month. After that a plateau of maximum involvement, extending from the 150th to the 238th day was evident. This was somewhat shorter than the period of maximum involvement observed in the female mice not ovariectomized. Moreover, in the ovariectomized series the extent of involvement was not as great, on the average, as in the normal females, and a much smaller number of mice died during this period. Eighteen, or 50 per cent of the non-sacrificed ovariectomized mice, as compared with 30 per cent of the normal mice, survived beyond 250 days. After 300 days the disease was more conspicuously regressive than in the normal females. The last 3 mice to die, namely, at 333, 343 and 349 days, had but slight persisting pulmonary tuberculosis. Acid-fast bacilli were at all times numerous after the first three months and on the average not more or less conspicuous than in the lungs of the non-ovariectomized mice.

Spleen: No great differences were seen from the type and severity of tuberculosis observed in the normal females.

Liver: There was a slight difference from the sequence seen in the normal females, in that some regression in extent of disease occurred in the animals surviving more than 280 days. Qualitatively the disease was similar in the two groups.

Kidneys: There was a difference in favor of the ovariectomized mice. In 66 per cent of the latter, as compared with 24 per cent of the non-ovariectomized mice no renal lesions were observed.

Ovariectomized Mice Treated with Estrogenic Substance

Forty-six animals were studied. Five died of intercurrent infections in the first three and a half months. The average length of life of the others, exclusive of those killed, was 206 days, distinctly less than that in the other two groups of this experiment.

Lungs: The course of infection was more like that observed in the non-ovariectomized than in the ovariectomized mice. Again a long plateau of maximum infection was apparent, as in both other groups, extending from the 150th to the 240th day. Only 5 animals, or 16 per cent of the non-sacrificed animals, survived beyond this period, as compared with 30

per cent in the non-ovariectomized mice and 50 per cent in the ovariectomized mice not treated with estrogenic substance. After 240 days some regression in the extent of tuberculous involvement was evident, but it was only in moderate degree, as in the non-ovariectomized mice, contrasting distinctly with the conspicuous regression seen in the ovariectomized but otherwise untreated mice. Acid-fast bacilli were always numerous, and at no time significantly different in number from those seen in the other two groups.

Spleen and Liver: Tuberculous changes were visible in those organs throughout the experiment and in extent were much like those observed in the non-ovariectomized mice. The regression in extent in the liver in the late phases of the disease observed in ovariectomized but otherwise untreated mice that lived 300 days or longer, was not observed. Of the animals in the series treated with estrogenic substance, only the 4 sacrificed two days later survived beyond 267 days.

Kidneys: In these organs involvement was rare. It was observed only during the first part of the period of maximum involvement of the lungs, and was always slight in degree.

Analytical Review of Experiment 1

Some differences in the course of tuberculous invasion in the three groups of black female mice were observed. Their significance is debatable. The most conspicuous variation in extent, severity and persistence of disease occurred in the lungs. In all three groups a period of maximum involvement was observable, extending from about the 150th to the 250th day. Prior to the 150th day the disease was increasing and after the 250th it was regressive. The animals that were ovariectomized and not treated with estrogenic substance appeared to have an advantage in respect to this healing process. A relatively high proportion survived to ten months or more, and in the last two months notable clearing of the pulmonary disease took place. However it is impossible to determine whether the animals lived longer because the clearing took place, or longer survival afforded more time for clearing. A relatively low mortality in one group, namely, the ovariectomized mice, during the period of maximum intensity of disease suggests that in some way ovariectomy was protective and estrus harmful. In no instance in any group, however, was the tuberculous process arrested. In the spleen, which appeared to be a continuing reservoir of infection in all groups, there was no conspicuous difference between the animals, regardless of treatment.

EXPERIMENT 2

FEMALE WHITE MICE

NORMAL, OVARIECTOMIZED AND OVARIECTOMIZED WITH SUBSEQUENT TREATMENT WITH ESTROGENIC SUBSTANCE

As in the case of the female black mice, approximately 150 mice were set aside for this experiment. The white mice were of the C strain of Bar Harbor. A few mice were lost in accidents or were discarded for failure to show typical response after ovariectomy or ovariectomy followed by treatment with estrogenic substance. They were approximately nine weeks old when infected. The animals finally used for the duration of the experiment were distributed as follows: normal, 42; ovariectomized and not treated, 45; ovariectomized and treated with estrogenic substance, 46.

The ovariectomized mice had been subjected to operation ten to fifteen days before infection, and control simple bilateral lumbar incisions were performed on the non-ovariectomized animals. All of the mice were infected intraperitoneally with 0.01 mg. of the Ravenel strain of bovine type tubercle bacilli on October 15, 1937. Estrogenic substance (1:6 dilution of aqueous theelin from Parke, Davis and Company), as in the case of the female black mice, was injected subcutaneously each day except Sunday in a volume of 0.1 cc. in the estrogenic substance group, for the first twelve months of the experiment, after which the treatment was discontinued.

As in the case of the black mice, several series of 5 mice from each group were killed to observe the progress of the disease at predetermined intervals. Series were killed at 56, 110, 181, 264 and 357 days and the survivors at 490 days. It was thought that in this way complication due to intercurrent infection would be avoided. This did not prove to be the case, however. Patches of chronic nontuberculous bronchopneumonia were not infrequent in apparently healthy mice. Examinations of the killed or dying mice were made exactly as in the case of the corresponding series of black mice.

The white mice differed notably from the black mice in their length of survival. As in the case of the black mice, certain quantitative differences in tuberculosis in the three groups were apparent, as indicated in tables 4, 5 and 6 and in the following summaries by organs.

Normal Females

Forty-two mice were studied. Only 7 died of intercurrent infection. The rest were killed, at the periods noted, for observation in comparison with ovariectomized, otherwise untreated mice, and ovariectomized mice treated with estrogenic substance.

TABLE 4

Normal female mice (C white) infected with 0.01 mg. bovine type tubercle bacilli—10/15/37

NUMBER	DATE OF DEATH	DAYS OF LIFE	DEGREE OF INVOLVEMENT			
			Lung	Spleen	Liver	Kidney
732	12/10/37*	56	0	2	1	2
734	12/10*	56	0	2	0	1
735	12/10*	56	0	2	0	—
736	12/10*	56	0	2	1	0
737	12/10*	56	0	1	0	0
738	2/ 2/38*	110	1	1	1	0
739	2/ 2*	110	1	2	1	0
740	2/ 2*	110	1	1	1	0
769	2/ 2*	110	1	1	0	0
770	2/ 2*	110	1	2	0	0
771	3/28*	164	1	1	0.5	0
741	4/14*	181	2	1	1	0
742	4/14*	181	2	2	1	0
772	4/14*	181	2	2	2	0
773	4/14*	181	2	1	0	0
774	4/14*	181	2	3	2	1
743	5/ 6*	203	3	3	2	0
744	7/ 6*	264	2.5	2	2	0
745	7/ 6*	264	4	3	1	0
746	7/ 6*	264	2	2	2	2
747	7/ 6*	264	3	3	1	1
748	7/ 6*	264	2	2	1	1
750	10/ 7*	357	3	2	2	0
751	10/ 7*	357	4	3	2.5	1
752	10/ 7*	357	4	2	2	1
753	10/ 7*	357	4	2.5	2	1
754	10/ 7*	357	3	2	1	1
775	10/19	369	3	1	2	0
776	11/ 9	380	3.5	—	—	—
760	11/10	381	6	2.5	2.5	1
761	11/23	394	4	2	1	3
755	1/25/39	455	3.5	—	—	—
756	3/ 1*	490	1	2	1	0
757	3/ 1*	490	3	2	1	2
758	3/ 1*	490	3	1	1	2
762	3/ 1*	490	2	3	0	0
763	3/ 1*	490	1	0	1	0
764	3/ 1*	490	0	1	1.5	0.5
765	3/ 1*	490	2.5	1.5	0	0
777	3/ 1*	490	3.5	1	1	1
778	3/ 1*	490	3.5	1	1	0
779	3/ 1*	490	3	0	1	0

* Killed.

TABLE 5

Ovariectomized female mice (C white) infected with 0.01 mg. bovine type tubercle bacilli—10/15/37

NUMBER	DATE OF DEATH	DAYS OF LIFE	DEGREE OF INVOLVEMENT			
			Lung	Spleen	Liver	Kidney
826	11/ 8/37	24	2	3	1.5	2.5
829	11/ 9	25	0	—	—	—
827	11/17	33	0	2	1	0
828	11/17	33	0	2	1	0
830	11/20	36	0	—	0	0
782	12/10*	56	1	1	2	0
783	12/10*	56	1.5	2	3	0
831	12/10*	56	2	3	3	0
832	12/10*	56	0.5	2	1	—
833	12/10*	56	—	—	2	0
784	12/13	59	3.5	6	2	0
785	12/19	65	2.5	6	3	0
786	1/ 6/37	83	2.5	4	2	0
787	1/22/37	99	2.5	3.5	1	0
788	1/25/37	102	3	3.5	2	0
789	2/ 2/38*	110	2	3	0	0
790	2/ 2*	110	1	2	2	1.5
812	2/ 2*	110	1.5	3	2.5	1
818	2/ 2*	110	1	3.5	2	1.5
825	2/ 2*	110	1	2	0	0
791	2/25	133	2	2	0.5	2
792	4/14*	181	1	2	0	0
793	4/14*	181	1	1	1	0
813	4/14*	181	2	2.5	2	0
814	4/14*	181	2	2	1.5	1
819	4/14*	181	2.5	2	0	0
794	5/23	220	3	2.5	1	0
799	6/24	252	2	3.5	0	0
795	7/ 6*	264	2.5	3	1	0
796	7/ 6*	264	3	2	2.5	1
797	7/ 6*	264	2	2	1	0
798	7/ 6*	264	3	3	2	1
815	7/ 6*	264	2.5	3	1.5	0
801	10/ 7*	357	2	3	1	0
802	10/ 7*	357	1.5	2	1	0.5
803	10/ 7*	357	1	2	1	0
804	10/ 7*	357	2.5	2	1	0
805	10/ 7*	357	2.5	2.5	1	0
822	2/10/39*	471	2	—	—	—
807	3/ 1*	490	4	2	1	0
808	3/ 1*	490	2	1.5	0	1
809	3/ 1*	490	3	1	1	0
810	3/ 1*	490	3	1	0	0
816	3/ 1*	490	0	2.5	0	0
817	3/ 1*	490	2	3	2.5	2

* Killed.

TABLE 6

Ovariectomized female mice (C white) treated with estrogenic substance, infected with 0.01 mg. bovine type tubercle bacilli—10/15/37

NUMBER	DATE OF DEATH	DAYS OF LIFE	DEGREE OF INVOLVEMENT			
			Lung	Spleen	Liver	Kidney
834	12/10/37*	56	0.5	2	1	0
835	12/10*	56	0.5	2	0	0
836	12/10*	56	1	2	1	0
837	12/10*	56	1	1	0.5	0
863	12/10*	56	1	1	2	1
838	2/ 2/38*	110	1.5	2	1	0
850	2/ 2	110	2	2.5	2	1
856	2/ 2*	110	1	2	2	0
862	2/ 2*	110	1	2.5	1.2	0
870	2/ 2*	110	1.5	2.5	0	0
876	3/ 2	164	4	2.5	1	1
878	4/ 6	173	2.5	1.5	1	1.5
839	4/14*	181	2	2.5	1.5	0
851	4/14*	181	2	3.5	2	1
857	4/14*	181	1	3	1	2
871	4/14*	181	1	1.5	0	0.5
877	4/14*	181	0.5	1.5	0	1
852	5/23	220	2.5	2.5	1	0
840	7/ 6*	264	3	2	1	1
841	7/ 6*	264	3	2.5	1	—
842	7/ 6*	264	3.5	2	0	2
843	7/ 6*	264	2.5	3.5	2	1
844	7/ 6*	264	3	2.5	0	1
858	8/11	300	2	3	1.5	1
845	9/13	332	2.5	2.5	1	2
873	9/18	337	3	2	0.5	0
872	10/ 7*	357	2	1	1.5	1
880	10/ 7*	357	2.5	1	1	0
881	10/ 7*	357	2	2.5	1.5	0
882	10/ 7*	357	4	2	1	0
883	10/ 7*	357	3.5	3	—	1
853	10/14	364	2	2	1.5	0
867	10/18	368	2.5	3	1	2
859	10/19	369	1	2	1	—
854	11/10	360	3	2	1	1
860	12/ 1	411	3	2	1	1.5
846	12/ 3	413	—	3	2	1
864	12/10	420	3	3.5	3	3.5
868	1/ 2/39	443	4	3	1.5	1
861	1/23	453	4	—	1	1
865	1/25	456	2	2	1	0.5
874	2/27	488	4	2.5	—	1
847	3/ 1*	490	3.5	2	1.5	1
848	3/ 1*	490	2	3	1.5	3
849	3/ 1*	490	2.5	2	1.2	1
869	3/ 1*	490	3	2	2.5	2

* Killed.

Lungs: No lesions were evident at 56 days. At 110 days tuberculous infiltration was approaching maximum extent. At 357 days the involvement was at its peak. In 4 mice dying of intercurrent infection during the next six weeks the infiltration was still maximal. In one of these, dead at 381 days, the most extensive invasion and largest number of bacilli found in the lungs in the entire investigation were observed.

On March 1, 1939, 10 animals, still surviving after 490 days, were killed. The tuberculous invasion was less extensive than in the mice killed or dying four months previously, and in most of them definitely regressive in character. In 3 of them it had practically cleared.

Spleen: Tuberculous invasion was clearly evident at 56 days and visible throughout the experiment, except in a few animals killed at 490 days. A plateau of maximum involvement extended from the 264th to the 357th day. Regression occurred after 357 days.

Liver: Some, but only slight evidence of invasion was seen at 56 days. From 181 to 381 days the tuberculous infiltration was maximal. After 381 days regression was evident. In 2 animals killed at 490 days no tuberculosis was found in the liver, although disease was still present in the lung and spleen.

Kidneys: More than half of the mice of the series gave no evidence of renal infection in the sections studied. Small lesions were seen in mice killed at 264, 357 and, in a few cases, at 490 days. An extensive tuberculous lesion was observed in a mouse dying at 394 days.

Ovariectomized Mice

Forty-five animals were studied. Fourteen died of intercurrent disease at various intervals, and the rest were killed in several series with representatives of the other groups of this experiment. Six mice were surviving at 490 days.

Lungs: Animals dying in the first month showed no pulmonary tuberculosis. In contrast to results in the series of normal females, tuberculous infiltration, although only moderate in degree, was evident at 56 days in all animals. In a group dying between then and 100 days still larger lesions were apparent, but the lungs were involved by intercurrent infection and it was impossible to determine the respective limits of the coincident infections, and, as indicated on page 199, the pyogenic infection may have stimulated the tuberculous process and increased its extent. At 110 days and 181 days tuberculous invasion was much less intense than in the non-ovariectomized females at the same periods.

At 264 days the involvement was at its peak for the ovariectomized series, but its intensity was still much less than that seen in the corresponding non-ovariectomized mice. At 357 days some regression appeared to have occurred. At 490 days clearing had occurred in a few mice; on the other hand, extensive infiltration, as advanced as any seen in the lungs in the entire course of the experiment, was seen in others.

Spleen: Involvement was variable throughout the experiment and occasionally of exceptional severity. Extreme tuberculous invasion, with myriads of bacilli present, was seen in 2 animals dying at about 60 days. In general, the disease seemed somewhat more severe in the spleens in this series than in the normal females.

Liver: In this organ also the involvement was variable during the sixteen months of the experiment and on the average somewhat more severe than in the normal females. There was definite decrease in intensity in the last four months. In 3 animals no disease was found at 490 days and in 2 of the other 3 killed at this period it was very slight.

Kidneys: Not much injury to the kidneys was observed in the series of ovariectomized animals. In three-quarters of them no tuberculosis was seen in the sections examined.

Ovariectomized Mice Treated with Estrogenic Substance

Forty-six animals were studied. Sixteen died of intercurrent disease, and the balance were killed for observation at the prescribed periods. Four animals were surviving at 490 days, when all remaining mice in the experiment were killed. Seven mice died with extensive tuberculosis between the 400th and 490th day.

Lungs: Slight tuberculous involvement was present in all animals at 56 days. No great increase in severity was evident at 110 days. A slightly greater amount was observed at 181 days. At 264 and extending to 357 days a plateau of maximum severity was apparent. The intensity at this time was much greater than in the ovariectomized animals not treated with estrogenic substance and somewhat less than that seen in the non-ovariectomized mice. In a few animals dying between the 357th and 490th day, slight regression appeared to have taken place, but the intensity of involvement was approximately as great in the mice killed at 490 days as at any time in the experiment.

Spleen: Tuberculous involvement was intense throughout the experiment, somewhat exceeding that observed in the untreated ovariectomized and non-ovariectomized mice.

Liver: As in the case of the spleen, tuberculous involvement was more extensive than in the other two series of animals in this experiment. No regression was apparent in the final mice of the series.

Kidneys: The kidneys were more frequently and often more severely damaged by tuberculosis in this series than in the normal females and untreated ovariectomized mice. Maximum involvement was observed in some of the animals living more than 400 days.

Analytical Review of Experiment 2

In several respects the results of experiment 2 confirmed those of experiment 1. Fortunately a relatively small number of animals died of intercurrent disease, so that comparable observations could be made on equal sized groups at various intervals. As in the black mice, a characteristic progression of pulmonary disease occurred. Within the first two months little disease was evident in the lungs. After that a slow increase in invasion was apparent. In comparable dosage, progress of the infection seemed to be slower than in the black mice, but ultimately a peak or plateau of maximum involvement was apparent for each series. In the normal white females, that is, the non-ovariectomized mice, this plateau was much more delayed than in the normal black females, a fact to be correlated with the longer survival of the white animals.

As in the black mice, the ovariectomized animals not treated with estrogenic substance fared better as regards pulmonary disease than the normal females. The proportion of animals in the plateau of maximum intensity was decidedly less than in the normal group and the tuberculosis of the plateau period was less severe. The same difference was observed between the ovariectomized mice, otherwise untreated, and ovariectomized mice treated with estrogenic substance. A corresponding, apparently favorable influence of ovariectomy was not seen in the spleen. This fact also corresponds with the observations in the black animals.

Tuberculous white mice of the C strain had a notably longer survival than black mice of the Bar Harbor C 57 strain. It was unfortunate that the two strains could not be compared in a single experiment. Breeding exigencies made it necessary to postpone the use of white mice until eight months after the black mice were inoculated. Thus, although the same strain of tubercle bacilli was used, and in the same dosage, the results cannot be compared with certainty. However, the very long survival of the white mice and the apparent vigor of a large surviving

percentage at 490 days, when it was decided to terminate the experiment, suggest strongly that the white mouse used was constitutionally more resistant than the black mouse.

It is to be noted, however, that in late periods of the disease in the white as well as black mouse active pulmonary tuberculosis was still present. In fact extensive tuberculosis, possibly representing a recrudescence in severity after a period of regression, was evident in some of the very old white mice.

EXPERIMENT 3

MALE AND FEMALE BLACK MICE

Fifty male and 50 female mice were used in this experiment. Unfortunately a laboratory accident, namely, excessive application of creolin as a disinfectant, destroyed three-quarters of the female mice. The remainder should probably be considered a selected lot and for this reason, as well as the paucity in number of females, the experiment cannot be looked upon as a reliable comparison of the course of tuberculosis in male and female mice. Hence the record of the experiment will be given briefly, rather than in detail, as in the report of the preceding experiments.

In this series no animals were killed for observation. The mice, as they died from whatever cause, were examined for the degree of tuberculosis present, as in the other experiments. The Ravenel strain of bovine type tubercle bacilli was used as previously. Although the infecting dose was the same, average survival was not as long as in the black mice of experiment 1. Intercurrent infection was extremely common, so that it was difficult to compare the extent of tuberculous lesions. There was some suggestion, based upon the great concentration of tubercle bacilli in pneumonic areas in which other bacteria could be seen, that nontuberculous pneumonia had a tendency to increase the extent of tuberculosis. It was not always possible to distinguish nontuberculous and tuberculous pneumonia, however. It is quite possible that in certain instances of suppuration in which acid-fast bacilli were exceedingly numerous they were themselves the cause of the suppurating lesion rather than bacilli growing freely in a region of suppuration due to other cause.

The average length of life was greater in the female than in the male animals, but this fact is probably not significant because, as already pointed out, the females were a selected lot freed from the weaklings by the creolin. The average intensity of tuberculous invasion was approxi-

mately the same in the organs of the male and female animals. Only minor differences were to be seen in tuberculosis of the viscera other than the lungs. In the latter organ, however, the male animals tended to show more of the characteristic terminal regression in the extent of pulmonary invasion than did the females. The extent of tuberculosis in the lungs of males in the middle period of the experiment, that is, from 140 to 180 days, was such as to suggest that tuberculosis was the cause of death. The deaths that occurred after this period were probably due as much to intercurrent pneumonia as the existing tuberculosis.

In the females, some of which lived to 281 days, pneumonia was so prevalent that it was impossible to determine the true extent of the tuberculosis, and the characteristic regression of pulmonary tuberculosis seen in the experiments already described was not observed.

EXPERIMENT 4

MALE AND FEMALE BLACK MICE, NORMAL AND CASTRATED

Experiment 3 was repeated with the addition of castrated male and ovariectomized female mice. Approximately 100 mice, divided in the four groups, were employed. The animals were infected when between sixty and ninety days of age. Again the Ravenel strain of tubercle bacilli in dosage of 0.01 mg. was employed. One set of 5 animals in each group was killed at 47 days to compare the extent of infection in the absence, insofar as possible, of intercurrent disease. Unfortunately in the succeeding period intercurrent disease became almost universal.

The characteristic course of tuberculosis as described in experiments 1 to 3 was observed in experiment 4. For a reason not clearly apparent the onset was more rapid, but a plateau of maximum invasion followed by some regression was observed. The regression was not as conspicuous as in animals of the several previous series.

One conspicuous difference from the other experiment was the great frequency of splenic amyloidosis. Hepatic amyloidosis was also observed occasionally. The deposit may have been related to the intense infection accompanying the tuberculosis.

Because of the complication of secondary infection and the corresponding short life of the animals, it will not be profitable to make a detailed comparison of the extent of tuberculosis in the four groups of animals. All animals died in less than three months. Among the mice killed at 47 days, some difference was apparent that may have been of significance.

There was somewhat less pulmonary tuberculosis at this stage in the normal males and ovariectomized females than in the castrated males and normal females.

As in experiments 1 and 2, the ovariectomized females outlived the normal females, and the average intensity of the tuberculosis was somewhat less. This was the one constant finding in the whole investigation.

No significant differences in the severity of tuberculosis were apparent after the 47-day observation in the normal and castrated males.

The duration of survival in this experiment was too short for observation of the plateau of maximum intensity of disease, which was apparent in experiments 1 and 2.

EXPERIMENT 5

MALE AND FEMALE BLACK MICE TREATED WITH PREGNANT MARE SERUM, NORMAL MARE SERUM, PLACENTAL EXTRACT AND ESTROGENIC SUBSTANCE

As a final experiment it was decided to determine, if possible, whether the gonadotropic hormones in the serum of pregnancy and the placenta exerted any detectable effect. Two hundred black mice of the Bar Harbor C 57 strain were used, divided into four groups of 50 mice, each in turn consisting of 25 males and 25 females. One group received the serum of a mare in the eighth month of pregnancy. Another group, serving as a control on the first group, received normal mare serum. We wish to express our thanks to E. R. Squibb and Sons, who kindly provided the normal and pregnant mare serum without charge. A third group received placental extract (emmenim from Ayerst, McKenna and Harrison). The fourth group was injected with the same estrogenic substance as was used in experiments 1 and 2, but in twice the previous concentration, that is, in a dose of two rat units per day (theelin from Parke, Davis and Company, in 1:3 dilution).

All animals were infected with 0.1 mg. Ravenel strain bovine type tubercle bacilli, that is, ten times the dose used in the preceding experiments. The serum and hormone preparations were injected subcutaneously daily, except Sunday, as in previous experiments, and in a volume of 0.1 cc. In this experiment the hormone injections were commenced a few days before infection.

The disease produced was more rapid in onset and more severe as a generalized process than that observed in the mice injected with 0.01 mg. of bacilli of the same strain. Whether because the severity masked differences or because there was no reason for a difference to occur, the tuberculosis induced did not vary significantly from group to group. Hence

the detailed protocols for the individual mice will not be given. In certain important respects the eight groups of animals behaved in a quite similar manner. In each group the majority of animals died within the third month. In almost all of the groups a plateau of maximum pulmonary involvement, followed by some regression, was apparent, as in the previous experiments. This occurred in most of the groups from about the 50th to the 75th day. In several groups (females treated with normal mare serum, females with theelin, females with emmenin, males with pregnant mare serum, males with theelin and males with emmenin) a few animals were alive at the end of four months. The experiment was terminated at this point by killing the surviving animals.

Pulmonary involvement was maximal in the series in both males and females treated with pregnant mare serum. However, there was enough variability within each group so that the apparent excessive degree of tuberculosis in the mice treated with pregnant mare serum might have been fortuitous.

Differences from the early experiment attributable to the larger dose were unmistakable. In addition to the relative brevity of life after infection and the increased speed of onset of the disease, a more massive generalization was apparent in the severity of tuberculosis in the spleen, liver and kidney. In the spleen, particularly, the disease was conspicuous. Unusually severe degree of involvement of the kidney was seen, and a higher proportion of cases of disease of this organ were noted than in most of the previous series.

SUMMARY

Female and male black mice and white mice treated in various ways were studied with respect to resistance to artificially induced tuberculosis. Black females (Bar Harbor C 57 strain) and white females (Bar Harbor C strain) behaved identically in regard to the course of tuberculosis in two parallel experiments in which resistance was compared in untreated females, ovariectomized mice and ovariectomized mice injected daily with estrogenic substance (theelin). In all three groups in each experiment a plateau of maximum pulmonary tuberculosis was evident in the mid-period of the life of the animals, lasting from about the 150th to the 250th day after infection. Following the 250th day the tuberculosis was regressive in most animals. Of the three groups in both the black and white series, the ovariectomized mice developed somewhat less severe tuberculosis at the height of the disease and showed more

regression of pulmonary involvement than either the untreated females or the ovariectomized animals treated with estrogenic substance. Differences in degree of involvement were most pronounced in the lungs. The reason for the seeming protective effect of ovariectomy was not apparent. The difference in extent of tuberculosis in untreated females and ovariectomized mice treated with estrogenic substance was negligible.

White mice appeared somewhat more resistant to tuberculosis than black mice in the two strains studied.

In another series of animals the resistance of normal and castrated black male and female mice was compared. The course of tuberculosis was exceptionally severe in all animals, however, and differences in favor of one or another group were not apparent.

In a final experiment, on the effect of the gonadotropic hormones of pregnancy, parallel groups of black mice were set up as follows for an additional study of the effect of sex hormones on resistance: untreated males and females, and males and females treated respectively with normal mare serum, pregnant mare serum and placental extract (emmenin). No significant differences in resistance were observed between males and females. The females treated with pregnant mare serum developed the severest tuberculosis of the several groups, but the difference from the general average of all groups was not outstanding.

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FREQUENCY OF TUBERCULOUS LESIONS AT AUTOPSY[1]

Some Epidemiological Inferences

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INTRODUCTION

Numerous investigations have been undertaken in recent years in an effort to shed light upon the relative and absolute frequency of tuberculous infection among groups of the general population in this and other countries. Routine serial X-ray examinations and tuberculin tests, for instance, of school children and more or less well defined groups of adults have been repeatedly employed in an attempt to advance knowledge about the actual dissemination of tuberculosis infection.

Few data of recent times, however, are available on the occurrence of healed or active tuberculosis in autopsy material from general hospitals. Old data are still frequently quoted as sufficient evidence for the high frequency of healed tuberculous infection. Naegeli (1) published in 1900 a careful report of 508 autopsies. Among persons eighteen years of age and over, 93 per cent were found to have healed, inactive or active tuberculous lesions in the lungs, while only 17 per cent of those under eighteen years exhibited positive findings. Naegeli's results were generally accepted and were later substantiated by other investigators. Some pathologists at the beginning of the century confirmed the high occurrence of tuberculous lesions among adults in autopsy material, for example, Burkhardt (2), while others, for example, Beitzke (3), found a somewhat lower percentage. Beitzke, however, agreed with other observers that practically all the adults in his hospital population exhibited demonstrable tuberculous lesions in the lungs. Thus, by the first decade of the century, it became generally accepted that all adults harbor in their bodies distinct pathological marks of tuberculosis infection.

In the following years, especially after the World War, not many observations of this kind were published. Reports on routine autopsies on soldiers (1914–1918) revealed in contrast to other studies only a very

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small percentage of tuberculous findings, and in 1919 Bushnell (4), among others, called attention to this discrepancy. Wason (5), who later discussed this point at length, gives as explanation for these findings: "(*1*) that the very careful methods of Naegeli, Burkhardt and Opie, rarely applicable in the field, would have revealed a much higher percentage of tuberculous lesions; (*2*) that in the more vigorous young adults comprising a large proportion of the army, tuberculous lesions were present in a much lower percentage or as such minute foci that they were not found." A similar explanation was advanced at the same time by Schirp (6). In 1922 the latter author reported on 238 autopsies of persons who died of various diseases. He found in 53 cases, from birth to one and one-half years of age, 3, or 5.6 per cent, with phthisical lesions; in 21 cases, one and one-half to eighteen years of age, 14, or 66.7 per cent; and in 164 persons, eighteen years old and over, 152, or 92.6 per cent, with positive findings.

In this country Opie (7) published in 1917 a careful study dealing especially with the location and character of tuberculous lesions. Autopsies were made upon 93 children (under eighteen years) and 50 adults (eighteen years and over). Evidence of tuberculous infection was found in the lungs of the 50 adults, whereas in the children the frequency of tuberculous lesions was much smaller, 23.7 per cent for the group as a whole but increasing steadily from 9.3 per cent in 43 autopsies of infants under one year of age to 6 positive findings in 9 autopsies of persons ten to eighteen years of age. Thus his results were in agreement with the European experience, especially that of Naegeli and Burkhardt.

In 1922 Wason (5) published an extensive report on the same subject. "In the 523 more complete examinations," the author states, "no special effort was made to search for tuberculous lesions, but the conditions of the pleura, the apices of the lungs and the lymph nodes were noted." The average percentage of adults (twenty years and over) in whom no evidence of infection was found was 18 per cent. Thus the percentage of positive findings, 82 per cent, is rather high although somewhat lower than that of Opie. The difference is possibly due, according to Wason's opinion, to a different technique in performing the routine autopsies.

In 1925 Lambert and de Castro Filho (8) reported on 402 autopsies performed in São Paulo, Brazil. They obtained for all ages together 72.8 per cent healed and active tuberculous lesions including a relatively high amount of doubtful lesions (32.3 per cent), "chiefly instances of more or less extensive pleural adhesions." Assuming that half the

"doubtful" lesions were tuberculous in origin, the percentage of positive findings amount, according to the authors, to approximately 60 per cent. On the other hand, as they state, "it is probable that a fair number of obsolete or healed lesions, such as an isolated calcified node or a small apical scar, were not recorded."

In 1927, Todd (9) published a survey emerging from serial examination of 404 corpses in Edinburgh. Of those, 18 died from tuberculosis. Among the 386 who died of other diseases, 266, or 69 per cent, showed definite signs of tuberculosis. Although this percentage is distinctly lower than that of Naegeli and others in former years, there is no reason to assume that in this careful search for tuberculous lesions an essential amount of positive findings has been overlooked.

This and the findings of Wason and of Lambert and de Castro Filho appear to indicate that since Naegeli's time a decrease in the frequency of healed tuberculous lesions is observable in persons who have died from diseases other than tuberculosis. This inference is borne out in a striking fashion by Wegat's study (10) which is not, however, strictly comparable to the preceding. Wegat analyzed the statistics on tuberculosis in 17,962 postmortem examinations made at the Pathological Institute of Düsseldorf (Germany) during the years from 1908 to 1931. He was concerned mainly with tuberculous findings in the bone system and omitted all cases where only a primary infection of lungs, which is of course the most important location regarding healed tuberculous lesions, was found. Wegat counted 3,588 positive cases in which active tuberculosis was present in some organ, or all together 20 per cent. After classifying the material according to year of autopsy he noted a very distinct drop in the frequency of positive findings, from 30 per cent in 1908–1912 to only 11 per cent in the period of 1928–1931. These results agree well with the inference which could be drawn from the review of the preceding studies that a decline has occurred in the frequency of cases showing pathological evidence of past tuberculous infection. This decline seems to parallel the decrease in the mortality from tuberculosis as reported by vital statistics.

At the time of Naegeli's observations tuberculosis mortality was extremely high in most European countries as well as in the United States, amounting to 200 or more deaths per 100,000 population. It will also be recalled that immediately after the World War, at the time of Schirp's observation, the tuberculosis mortality in Germany, especially, had returned almost to this high level. The marked decrease in the mortality

from this disease set in after the war, and when Todd made his survey the tuberculosis mortality in Scotland was only one-half of what it had been at the beginning of the century (11). Thus, if the decrease in healed lesions and mortality is more than purely coincidental, it is reasonable to expect that now, following a period of uninterrupted decline in tuberculosis mortality, one no longer will find the same high frequency of old healed primary foci in the lungs as was observed at the beginning of the century. It is with a desire to investigate further this question that this study on the frequency of tuberculous lesions at autopsy was undertaken.

A comparison of more recent autopsy figures with the results of the first mentioned surveys is pertinent, since it would provide the worker in the field of tuberculosis with some factual data important in the discussion of changes in the epidemiological character of the disease and perhaps indicate some more practical conclusions for the further campaign of prevention.

THE PRESENT AUTOPSY RESULTS

The postmortem examinations have been performed in the Washington County Hospital, Hagerstown, Maryland, by the same pathologist during the last two years (from September 1, 1938 to August 31, 1940). In the main, the findings reported result from macroscopical examination. A careful search of lungs and hilar lymph nodes will lead to the discovery of calcified lesions even if they are small. Histological examinations of the tuberculous areas have been made occasionally, but on the whole it was the gross appearance more than anything else which was relied upon for diagnostic purposes. The special conditions of a small city do not allow any delay in the final delivery of the corpse to the undertaker and still less the removal of whole organs from the body as a routine procedure. Hence it has not been feasible to take X-ray pictures of the lungs studied at autopsy. Bacteriological examination of the foci for virulent tubercle bacilli by animal inoculation did not fall within the scope of this study.

Cases have been listed as questionable where small, grayish, firm subpleural or intrapleural scars without calcification but with overlying old fibrous adhesions suggested a tuberculous origin. In these infrequent instances, as will be seen later, microscopical examination usually failed to disclose any conclusive evidence for or against an old tuberculous focus. Old fibrous adhesions alone, apical or otherwise, have been rated

as negative in this survey, in accordance with most of the former investigators. It may be mentioned in this connection that, in spite of careful search, an abdominal primary focus has been found only once. This low incidence was unexpected, especially in view of the fact that a semirural population was dealt with.

The limitations just mentioned are counterbalanced by the following two factors: First, the material originates from a semirural population which has been selected as typical and still is used for other surveys by the United States Public Health Service. Most of the patients treated in the Washington County Hospital either have been born and have lived their whole lives in the county or have spent the greater part of their years here or in neighboring counties. The autopsies represent an average of slightly over 45 per cent of the deaths occurring in the hospital during the two years of the survey. They are the result of the endeavors on the part of the staff members and the pathologist to secure autopsy permits in as many instances as possible without any selection as to cause of death or other factors. Thus it may safely be assumed that the autopsy material really gives a fair cross section of the dying population. This also holds true for the economic background of the patients who represent every social stratum. Furthermore, the hospital, a privately endowed nonprofit institution, does not admit patients with open tuberculosis. The physicians, in coöperation with the county and city health officers, have ample opportunity to diagnose cases with open active tuberculosis at a rather early stage and to send them nearby to the Maryland State Sanatorium for tuberculosis patients. Consequently, tuberculosis as a cause of death is rare among this group. The same considerations also apply to autopsies performed for medico-legal and other reasons on nonhospitalized persons. Thus this survey is based on an unselected material representative of a rather stable white population as it only can be collected in smaller communities.

The total number of autopsies performed was 176, 11 of which were discarded—8 because they were not complete, the examination being limited to one body cavity only, and 3 were autopsies of premature or stillborn babies. Thus the survey proper covers 165 autopsies among which there were 65 with tuberculous findings, or 39.4 per cent. It may be mentioned that this percentage for all ages is almost exactly half of Naegeli's findings, 79.9 per cent for his total autopsies. Thirty-two of the present postmortem examinations have been performed on infants and children up to ten years of age, among them 21 under one year of age.

Two of these, one white boy of eighteen months and one colored boy of thirteen months, died of tuberculous meningitis. The remaining 9 children, whose deaths were due to various causes, were free of evidence of a tuberculous infection; 133 of the postmortem examinations were on persons between the ages of ten and ninety years. The age distribution of the total material is given in table 1.

Only 5 members of the colored race are included in the whole group. Since differences according to race will not be touched upon later in this paper, suffice it to say that only the one colored male of the group showed a healed primary tuberculous complex whereas the 4 females did not.

TABLE 1

Age distribution of 165 autopsies at Hagerstown, Maryland, 1938–1940

AGE IN YEARS	AUTOPSIES	
	Number	Per cent
Under 1	21	12.7
1–9	11	6.7
10–19	5	3.0
20–29	6	3.6
30–39	16	9.7
40–49	18	10.9
50–59	30	18.2
60–69	28	17.0
70–79	18	10.9
80 and over	12	7.3
All ages.....	165	100.0

The small numbers of the material forbid any too meticulous analysis. In the following summary the autopsies performed on persons ten years and over are subdivided according to sex; the incidence of positive and negative findings of healed tuberculosis is given in absolute numbers and percentages.

Counting the questionable cases as negative, one arrives at a total figure of 133 autopsies of persons, ten years and over, with 63 positive findings for both sexes together, or a percentage of 47.4. The corresponding percentage for males is 44.4, for females 53.5; some more details as to sex and subdivision of tuberculous findings are given in table 2. If we take into consideration only the ages between twenty and ninety years, close to Naegeli's, Burkhardt's and Opie's age delimitation for adults, the percentage of positive findings does not change markedly. There

were 62 positive cases among 128 autopsies, or 48.4 per cent, as can be seen from table 3 in which the autopsy results are arranged by age decades. However, if the 4 active cases of tuberculosis are entirely left out in order to get, in accordance with Opie and Todd, the incidence of tuberculous lesions among those adult persons who have died of other diseases or an "index of the frequency of infection in the general population," the percentage decreases to 46.8. On the other hand, considering

TABLE 2

Tuberculous lesions in 133 autopsies of persons ten years and over, by sex

TOTAL AUTOPSIES	MALES		FEMALES		BOTH SEXES	
	Number 90	Per cent 100	Number 43	Per cent 100	Number 133	Per cent 100
Old healed lesions	37	44.4	22	53.5	59	47.4
Active tuberculosis:						
Fatal	1		—		1	
Concomitant	2		1		3	
Questionable cases	3	55.6	2	46.5	5	52.6
Negative cases	47		18		65	

TABLE 3

Tuberculosis findings in 165 autopsies by single age groups, Hagerstown, Maryland, 1938–1940

	AGE GROUPS IN YEARS									ALL AGES
	0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80+	
Total autopsies	32	5	6	16	18	30	28	18	12	165
Old healed tuberculosis	—	1	—	7	9	10	14	10	8	59
Active tuberculosis	2	—	—	1	—	2	—	—	1	6
Questionable cases	—	—	—	—	1	1	3	—	—	5
Negative cases	30	4	6	8	8	17	11	8	3	95

the 5 questionable cases also as positive, the incidence among adults rises to 50.8 per cent. Generally speaking, we may derive from the present autopsy findings that approximately 50 per cent showed distinct marks of tuberculous lesions as compared with nearly 100 per cent positive findings in the investigations of Naegeli, Burkhardt and Opie some twenty-five to forty years ago.[2]

[2] It may be added that, since September 1, 1940 up to May 31, 1941, 64 additional autopsies have been performed which show approximately the same percentage of positive tuberculous lesions by age distribution.

Arrangement of the present positive and negative findings according to age decades is shown in table 3. On account of the small numbers in the single age groups we have not computed percentages of tuberculous lesions by decades. However, the general upward trend is obvious. There occurred out of 32 autopsies in the age group from birth to nine years only 2 positive findings; out of 5 in the decade ten to nineteen years, one; and in the next, twenty to twenty-nine years, none. The latter results may be worth mentioning and possibly may have something to do

TABLE 4

Anatomical distribution of 59 positive tuberculous lesions

1. LUNGS			
Solitary, calcified foci *without* hilar lymph node involvement			
Right upper lobe	9	Left upper lobe	9
Right middle lobe	1	Left lower lobe	3
Right lower lobe	9		
Solitary calcified foci *with* hilar lymph node involvement			
Right upper lobe	4	Left upper lobe	8
Right middle lobe	—	Left lower lobe	9
Right lower lobe	2		
Multiple calcified foci *with* hilar lymph node involvement			
Right upper lobe			1
Right upper lobe and left upper lobe			1
Right lower lobe and all remaining lobes			1
Calcified primary focus with *active secondary* spread			
Left upper lobe calcified, right lower lobe active fibrotic			1
2. MESENTERY			
Calcified glandular solitary focus			1

with the often discussed postponement of fatal tuberculosis to later ages. Of course, these autopsy figures are much too small to allow far reaching conclusions. From the age decade thirty to thirty-nine years, however, there appears a definite jump in the amount of positive findings and even a slight upward trend in the following age groups, the tendency of which is in agreement with all former investigations. In the age group thirty to thirty-nine years, and forty to forty-nine years, half of the autopsies were positive, that is, out of 16 and 18 autopsies 8 and 9 were positive, respectively; in the decade fifty to fifty-nine years, out of 30 autopsies 12 were positive; in the sixty to sixty-nine year age group, out of 28

autopsies again half of them were positive; in the seventy to seventy-nine group, out of 18 autopsies 10 were positive; and in the highest age group, eighty years and over, out of 12 autopsies 9 were found with positive tuberculous lesions (see table 3). If we consider also the 5 questionable cases as positive, the slight upward trend in the higher age brackets becomes somewhat more distinct.

Some details concerning the anatomical distribution of the tuberculous foci and the secondary hilar involvement may be gathered from the summary given in table 4. The multiple calcified foci represent remnants of a more extensive infection with a healed secondary spread to other lobes of the same or contralateral lung. This extension was of active fibrotic nature in one case, whether in the form of exogenous or endogenous reinfection is without particular interest here. The death of the patient was in no way related to his tuberculous reinfection but to an arteriosclerotic gangrene of the leg with terminal pulmonary emboli.

As regards the "case-finding value" of the present autopsy series, it may be mentioned that in 3 instances the postmortem examination uncovered information about the presence of an active tuberculous infection, not known beforehand, which led to subsequent medical examination of the surviving family groups. Although based on a relatively small sample, this finding of 2 per cent of active unknown cases of tuberculosis indicates that autopsy records are a more valuable source of information to health departments than is generally recognized.

DISCUSSION AND EPIDEMIOLOGICAL INFERENCES

The foregoing findings of almost 50 per cent of healed tuberculous lesions among adults (40 per cent among all ages) of an unselected hospital population in a semirural county indicate that even to-day the frequency of tuberculous manifestations in the population is considerable. The people dealt with in this investigation have died in the hospital from diseases other than tuberculosis, but half of the adults exhibited distinct pathologic-anatomical signs of more or less healed tuberculosis. Assuming in agreement with the above quoted earlier surveys that the frequency of healed tuberculous lesions found at autopsies of unselected hospital cases represents an approximate yardstick of tuberculous *Durchseuchung* in the average living population, we would arrive through our present survey at a frequency of 40 to 50 per cent of tuberculous manifestations. This is still large when compared with the mortality from tuberculosis at the present time. It clearly demonstrates that

by far the largest part of the group infected by tuberculosis overcomes its infection entirely. If we assume a death rate from tuberculosis (all forms) of around 50 per 100,000 living in the United States at large (this figure is in close accordance with the official Mortality Statistics of the Census Bureau for the last years) and if we relate this death rate to the half of the adult population, which, according to our assumption, is infected, we get a ratio of 1:1,000. If we relate the above death rate to the infected proportion of all ages (40 per cent according to present autopsy findings), we get a still closer quantitative approach. The ratio then increases to 1.25:1,000. In other words, of 1,000 persons infected with the tubercle bacillus and affected to such a degree that anatomical lesions arose, only 1 to 1.25 person is doomed to die within a year from the disease.[3]

A similar consideration for the time around the turn of the century is of interest. According to the findings of Naegeli from Zürich (1900), Burkhardt from Dresden (1906), and of Opie from this country somewhat later, there were between 92 and 100 per cent tuberculous lesions in a large number of adult persons, who had died of various diseases at a hospital. If we are entitled to transfer these results to the general population—as has been done by the authors just mentioned and all those who were interested in the epidemiological inferences of the anatomical findings—it means that practically all adults demonstrated in their bodies macroscopical evidence of tuberculous lesions. These classical findings of pathology, indeed, along with the positive reactions to tuberculin tests, encountered since Pirquet's discovery of hypersensibility in infected individuals of all ages, were mostly taken as proof that almost everyone in his lifetime had undergone an infection with tuberculosis and that the tubercle bacillus as the causative agent may be considered a constant or ubiquitous factor in human surroundings. We may quote in this connection Opie (7a) who concludes his survey as follows;

[3] A further approach would be to relate the death rate of the adult population (twenty years and over) to the assumedly infected part of the adults. To find out this death rate is somewhat more difficult since the age composition of the population in different calendar years for the respective registration areas is not always at hand. However, in 1935, when the death rate from tuberculosis for all ages was given as 55.0 per 100,000 for the United States, the death rate for the ages twenty years and over could be computed at 77.0 per 100,000 from the official Mortality Statistics. Assuming a proportional decrease as in the total death rate (from 55 to 50), one arrives at a ratio of 1.4:1,000. These ratios do not much differ among themselves, and, as will be seen later, it does not matter at all for the problem of the relative diminution of the tuberculosis risk.

"Almost all human beings are spontaneously 'vaccinated' with tuberculosis before they reach adult life."

Thus it might well be justified to assume a frequency of tuberculous lesions in the general population of the United States around the beginning of the century similar to that observed in Europe. As a matter of fact, tuberculosis mortality was at that time of the same level or somewhat higher here than in England, Prussia, Italy and the Netherlands, to choose only a few European countries (11). The death rate from tuberculosis in the United States Registration area amounted in 1900 to 201.9 per 100,000 living. Thus, if we assume for the simplification of the sample a death rate of 200 per 100,000 and the frequency of tuberculous lesions as 100 per cent for adults and 80 per cent for all ages (inclusive of childhood) we obtain a ratio of 2:1,000 or 2.5:1,000, respectively, for the infected people. If we were able to compute, correspondingly, the death rate for adult ages alone in the Registration area of 1900, the ratio would probably increase to around 2.8 per 1,000. This is obvious if we review the age specific death rates at this time for the ages above twenty. They vary from around 250 to 320 per 100,000 in the different age groups. Since all the adults are supposed to be infected, the rate of 2.8 per 1,000 or 280 per 100,000 for the combined ages twenty years and over is probably a relatively good approach. In other words, the risk of dying from tuberculosis among the infected and already pathologically marked individuals was at the beginning of the century twice the ratio found four decades later.[4]

Expressed in simple probability terms the results read as follows: The risk of a person to become infected in the present population is one-half of what it was in 1900; the risk of an infected person to die from tuberculosis within a year is at present also one-half of what it was in 1900. Therefore, the risk of becoming infected and dying within a year equals one-fourth of the risk in 1900. This is, of course, demonstrated by the official mortality figures. It may be added that, in 1938, for the total United States, the death rate for both sexes from tuberculosis is given as 48.9 per 100,000 population; for the State of Maryland, 78.7; for Washington County, 46.6 per 100,000 of the corresponding population.

[4] It does not matter if we choose for this comparison the adult ages from twenty years and above or all ages together since the percentage decrease of tuberculous lesions in childhood is almost the same as in later ages, and also the decrease of tuberculosis mortality for all ages (from around 200 to 50) corresponds to that for adults alone (from around 280 to 70 per 100,000 living).

For a better insight into the tuberculosis problem we may thus be entitled to distinguish clearly between two main items responsible for the striking decrease of tuberculosis mortality since the turn of the century. First, if conclusions derived from the autopsy findings of the present investigation hold true for the general population, the number of infected persons with distinct pathological lesions has diminished by one-half. This result has to be confirmed by further and larger postmortem investigations, if possible from different states, before general conclusions may be drawn. However, it would seem that our methods in preventing the outbreak of tuberculosis as measured by the rather objective criterion of pathologic-anatomical absence or presence of specific tuberculous lesions have been fully successful in one-half of the populations. If this can be accepted as logical then the potential sources of infection have been essentially reduced.

Second, among those who are still to-day found to be infected with tuberculosis and already demonstrate significant pathological lesions, healed, calcified or not yet fully subsided, the risk of dying from open tuberculosis is at present only half (1–1.4:1,000) of what it was at the turn of the century (2–2.8:1,000). This second inference means that distinctly infected persons (the "tuberculous" in the widest sense) have at present twice as good a chance to survive and to be cured of tuberculosis as was the case in 1900. This may be registered as a success of modern therapy in the widest sense. Whether this reduction of tuberculosis mortality among infected people has been achieved by medical means and segregation of tuberculous patients in hospitals, by improvement of social conditions, or by whatever factors may influence the course of tuberculosis is hard to analyze quantitatively.

In this connection we may quote a very interesting discussion of the case fatality rate in tuberculosis. Drolet (13) in a recent investigation could not demonstrate any decrease of case fatality rate during the past twenty years in various large communities (New York, Chicago, Philadelphia, Detroit, etc.) when he defined this rate as the "annual ratio of deaths to new cases of tuberculosis reported." Thus he came to the conclusion, considering the obvious decline of tuberculosis, "that the preventive aspects of isolation in tuberculous hospitals have been far more effective than those arising from sanatorium or medical treatment." In a reply to Drolet's statements, however, Bogen (14) objected to his definition of case fatality rate and came, on the basis of his own computations, to an opposite conclusion: "The decrease in the average annual

case fatality ratio, disclosed by taking into consideration the delay between the notification of diagnosis and of death, agrees with that suggested by the increased age at death and by the prolonged survival time in the available data, as well as with general clinical experience. This finding is just as definite and important as the decrease in the general mortality rates from tuberculosis."

Both papers are worth reading in order to get a better insight into the arguments discussed. There is no question that increased hospitalization plays a very important part in all measures of preventive medicine during the last few decades. The same is true of other infectious diseases. But it seems to be more or less a matter of definition if we call the segregation of open cases in hospitals a measure of preventive medicine or medical treatment. Anyway, hospitalization belongs to modern therapy and is again only one part of the large social environmental factor, the change of which in modern times is supposed to have influenced the course of tuberculosis more than anything else. Yet it will always be difficult to weigh quantitatively against each other the significance of the different subgroups in the large social complex (nutrition, housing, occupation, education, hospitalization and therapy, size of family and other population factors).

It is not the intention here to enter into a discussion of the possible aetiological factors in the tuberculosis problem. That has been done in an earlier investigation (Wolff) where the specific, the hereditary and the social factors have undergone a critical analysis (12). But it seems obvious from the foregoing considerations based upon pathological findings in a new autopsy survey that preventive as well as therapeutic measures have equally contributed to the decrease of tuberculosis mortality during the last forty to fifty years. The sources of infection have been definitely reduced in the general population and the infected people have been better taken care of.

There is another point worth mentioning. Considering the age distribution of the positive findings in the present autopsy series (table 3), it was evident that in childhood and adolescence the incidence of tuberculous lesions is strikingly lower than in the higher ages. This was to be expected in view of the chronic character of the infection and in accordance with similar experience of former tuberculosis research. Especially among newborn babies and infants in the first year of life, the percentage of tuberculous lesions in large series of autopsies has been repeatedly found to be very small (Beitzke (3), Hamburger (15), Woll-

stein (16) and others). In the present investigation there were, out of 21 autopsies performed on infants in the first year of life, no tuberculous findings at all; out of 11 autopsies of children one to nine years of age only 2 with positive tuberculous manifestations; out of 5 autopsies of persons ten to nineteen years of age only one and of 6 autopsies twenty to twenty-nine years of age, none with positive tuberculous manifestations. Since the absolute figures become small when divided by age groups, we have not computed percentages by decades. However, if we class the ages up to puberty and after into three main groups (from birth to nineteen, twenty to forty-nine, and fifty and over) we may be better entitled to compute the respective percentages for these larger age groups (table 5).

TABLE 5

Total number of autopsies and positive tuberculous lesions, by three main age groups, in Hagerstown, Maryland, 1938–1940

AGE IN YEARS	TOTAL AUTOPSIES	POSITIVE TUBERCULOUS FINDINGS	
		Number	Per cent
0–19	37	3	8.1
20–49	40	17	42.5 } 48.4
50 and over	88	45	51.1 }
All ages.....	165	65	39.4

The summary in table 5 makes it obvious that the frequency of tuberculous lesions increases distinctly from childhood to the higher ages. From 8.1 per cent in the group of children (from birth to nineteen years) it jumps to 42.5 per cent in the twenty to forty-nine year groups and rises still higher in the ages over fifty years. The most striking feature in this summary as compared with the figures of former research workers is that after puberty has been reached the frequency of positive findings in all adult ages together amounts to 48.4 per cent, or almost exactly half of what Naegeli found in his initial investigation of the problem. But also the much smaller frequency of positive findings in the ages up to puberty has diminished to approximately the same degree; it is with 8.1 per cent scarcely half of what it was in the above mentioned investigations.

In this respect the observations of Wollstein and collaborators from the New York Babies Hospital deserve especially to be quoted. In three consecutive surveys they found in large numbers of autopsies, performed in children up to five years of age, a remarkable reduction of

tuberculous lesions. Out of 1,131 autopsies in the period from 1889–1908 there were 185, or 16.4 per cent; out of 1,320 autopsies in the years from 1908 to 1914 there were 178, or 13.5 per cent, and in the last survey for the years from 1914 to 1920 out of 2,024 autopsies only 184, or 9 per cent, which disclosed tuberculous lesions. These observations reveal a course strikingly parallel to the reduction from Naegeli's findings in 1900 to our findings forty years later and are the more valuable since they are made at the same place. Thus we may be justified indeed in saying that the reduction of tuberculous lesions concerns all ages equally.

In closing we may quote from Frost (17, 18) who, in two papers published in 1935 and 1937, when discussing the outlook for the eradication of tuberculosis, arrived at very similar conclusions without having the evidence of new autopsy findings: "Tuberculosis also differs from the other directly transmitted respiratory tract infections in that its mortality has declined consistently for the last fifty years or more and continues to decline in every part of this country for which adequate statistics are available. It is not directly established by comparable statistical evidence that there has been a proportionate decrease in the prevalence of infective cases of the disease, taking into consideration not only the number of cases but duration of the open stage. However, there appears to be no good reason to doubt that the prevalence of open lesions effective in spreading the tubercle bacillus has diminished progressively, and continues to diminish in each considerable period of time."

Such a diminution of tuberculous lesions is indicated by the present autopsy findings and by the trend of the cited observations since the World War in several countries. Since the reservoir of people infected with tuberculosis becomes smaller and smaller, the steady and proportionally greater decrease of the mortality rate during the last four decades is more easily explained. However, it must not be overlooked that, according to present autopsy records, the reservoir of adults infected with tuberculosis at one time or another in their lives still amounts to half of the population. Therefore, tuberculosis can still flare up again whenever external conditions turn to the worse for the bulk of the people. Without such a reverse there exists hope that further efforts in the campaign against tuberculosis will some day lead to a complete eradication of the white plague.

SUMMARY

1. The present survey on tuberculous lesions covers 165 autopsies performed in the Washington County Hospital, Hagerstown, Maryland,

on persons of all ages who died of various diseases. The incidence of positive findings in the adult ages, twenty years and over, which age delimitation is close to that of former investigators, amounts to 62 among 128 autopsies, or a percentage of 48.4. On the other hand, the childhood frequency is small, with no tuberculous manifestation in infancy and an incidence of only 3 positive findings among 37 autopsies in the combined ages of from birth to nineteen years, or a percentage of 8.1.

2. On the basis of these findings, as compared with former investigations in Europe and the United States (Naegeli, Burkhardt, Opie, Wason, Todd), it may be assumed that the number of infected and pathologically marked persons has been greatly reduced, namely from almost 100 per cent at the turn of the century to around 50 per cent at present, among an unselected hospital population. If this reduction of the potential sources of infection can be substantiated by pathological findings from larger population groups, it would indicate a real success of preventive medicine and public health activity in the fight against tuberculosis.

3. Taking, moreover, into account the still greater decrease of the death rate from tuberculosis during the same period, in this country from around 200 at the beginning of the century to around 50 per 100,000 in the last years, the percentage decrease of tuberculosis mortality is twice as high as the reduction of infected people. We may be justified, therefore, in assuming that the infected proportion of the population exhibits a considerable diminution of tuberculosis mortality. It seems probable that the risk of an infected person to die from tuberculosis has been reduced from 2–2.8:1,000 to 1–1.4:1,000, or by one-half, during the period under observation. This might be interpreted as representing, on the other hand, the results of therapy in a broad sense, improvement of social conditions, and the possible change of other factors involved in tuberculosis epidemiology. From this analysis the conclusion is suggested that the decrease in tuberculosis mortality is caused by the reduction of the sources of infection and, to an equal extent, by the treatment of infected persons.

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PULMONARY HISTOPLASMOSIS[1]

Report of Two Cases

HENRY E. MELENEY

Histoplasmosis of Darling (1), which has been given the more accurate but cumbersome name of "reticuloendothelial cytomycosis" by Humphrey (2), is a disease of protean manifestations. In its acute form it is a systemic infection of the reticuloendothelial cells of the body simulating kala-azar (3). It has also appeared in the form of a chronic skin disease (4), a mucous membrane and lymph node disease (5), and an infection apparently limited to the adrenal glands (6) and to the lungs (7). It has also been found as a spontaneous disease in a dog (8) and a ferret (9). Most of the cases have been diagnosed from histological sections at autopsy, but a few have been diagnosed before death and the causative fungus, *Histoplasma capsulatum*, first cultivated by DeMonbreun (10), has been studied extensively and its biological characteristics defined (11). One of the interesting features of the infection is the similarity of the more chronic lesions to those of tuberculosis and the occasional association of tuberculosis with the disease (6).

The two following cases, which were mentioned briefly by the author in a review on histoplasmosis (12), are reported in detail because of their interesting pulmonary features and because it is probable that the infection is not uncommon and will be found much more frequently if it is kept in mind by clinicians and pathologists.

Case 1: I. M., Vanderbilt University Hospital No. 98056, white male, age sixty-nine, a farmer from Middle Tennessee, was admitted on April 4, 1939, with a diagnosis of benign hypertrophy of the prostate, cystitis, pyelonephritis, arteriosclerosis and cardiac insufficiency. His temperature on the day of admission ranged between 99.4° and 102°F. but fell to normal in two days and remained normal until three weeks later. Physical examination showed nothing of note besides the evidence of an ascending renal infection, slightly increased systolic blood pressure and emphysema of the lungs with transient atelectatic râles over both lung bases. His blood showed 3,800,000 red blood

[1] From the Department of Preventive Medicine and Public Health, Vanderbilt University School of Medicine, Nashville, Tennessee.

cells with 9.5 g. haemoglobin, and 14,000 white blood cells with 91 per cent neutrophiles. His urine contained albumin, pus and a few red blood cells. The nonprotein nitrogen of the blood was 120 mg. per cent. The Kahn reaction was negative.

Nine days after admission a cystoscopy was performed and a catheter inserted for continuous drainage. The urinary infection showed gradual improvement, the nonprotein nitrogen of the blood fell to normal and the leucocyte count dropped to normal limits. On May 1, the patient was allowed up in a chair. On May 8, he complained of sharp, stabbing pain in the right axilla, and a pleural friction rub was found in this area. An X-ray film of his lungs showed multiple, sharply circumscribed shadows in both lungs, more on the right, interpreted as due to metastatic malignancy. There was also extensive fibrosis at both bases and an irregular density in the left base apparently due to pneumonitis. There were also several small, scattered calcified areas apparently due to old tuberculosis. For two weeks previous to this, his temperature had risen daily to about 99.8°F. with a few higher peaks, the highest being 101.6°F. On May 12, a gastrointestinal X-ray series was performed with the possibility of discovering the source of the supposed metastatic nodules in the lungs, but nothing was discovered. On May 15, examination of the chest showed evidence of pneumonitis at the right base, and on May 18, pleural friction rubs were present over both lower lobes. The temperature gradually rose until it fluctuated between 100° and 102°F., the white blood cells rose to 12,800, the lung signs varied from day to day, the friction rubs disappeared but the signs of consolidation increased somewhat. On June 10 an X-ray film of the chest showed the following changes: the entire lower two-thirds of the right lung field showed a rather homogeneous density, more marked in the lower third. In the left base there was a band of increased density above the costophrenic angle between the heart and chest wall. Inferior to this, in the angle, there was some rarefaction. Above the band there was scattered, irregular, fine infiltration. (See figure 1.) In view of the previous film which showed multiple small nodules, these changes were thought to be due to metastatic malignancy. The haziness in the right lung was apparently due to pleural involvement and some associated fluid. The patient gradually grew weaker and died on June 23.

Autopsy revealed prostatic hypertrophy, cystitis, pyelonephritis, slight hypertrophy of the heart and atheroma and partial calcification of the aorta. The right pleural cavity was entirely obliterated by a partly organized fibrinopurulent exudate. The left pleura presented a small area of adhesion on the lateral surface of the left lower lobe which, when broken, exposed a small cavity in the lung containing whitish granular material. The right lung showed a few areas of pneumonitis at the base of the lower lobe and many small, hard nodules which appeared to be tubercles. The left lower lobe was almost

completely atelectatic. On its lateral margin were a few nodular areas, 1 to 5 cm. in diameter, the largest being associated with the cavity mentioned above. The nodules contained a yellowish white material and at their periphery presented a fungating or papillary appearance. The liver was somewhat smaller than normal. It contained a few scattered tubercle-like areas and seemed to be somewhat fibrosed. The spleen was normal in size and appearance except that some fibrosis was present.

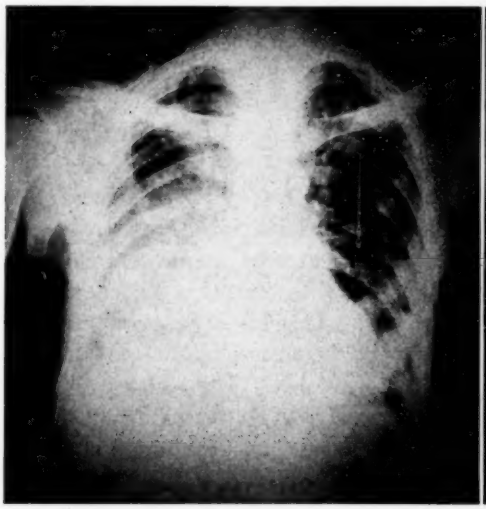

FIG. 1

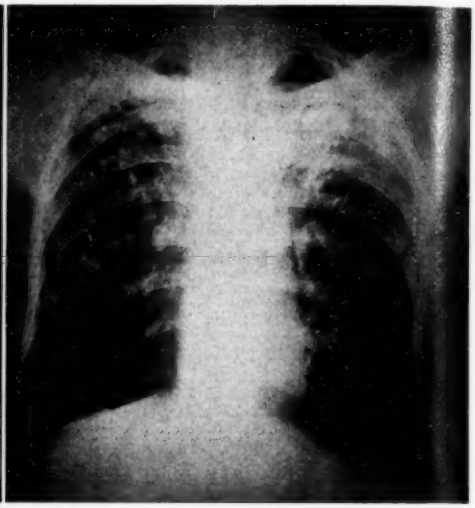

FIG. 2

FIG. 1. Case 1. Second X-ray film of lungs, June 10, showing homogeneous density in the lower two-thirds of the right lung field; at the left base a band of density between heart and chest wall with irregular, fine infiltration above, old calcified nodules in both lung fields and calcification of hilar lymph nodes.

FIG. 2. Case 2. X-ray film of lungs showing a large cavity in the left apex and a smaller one in the right, with infiltration in both upper lobes and a few scattered calcified nodules.

Microscopical examination showed the fibrinopurulent exudate on the pleural surface undergoing organization. The exudate was mostly amorphous with many nuclear fragments but relatively few normal cell elements. The lymphatics of the pleura were distended and some contained large mononuclear cells filled with parasites. These parasites were round or oval, averaged 3 μ in diameter, and consisted of a central blue-staining mass, round or crescentic in shape, and surrounded by a clear zone and a slightly refractile capsule. Morphologically this is typical of *Histoplasma capsulatum*. In the parenchyma of the lungs the nodules consisted of a central caseous area sometimes broken down into a cavity, the caseous material consisting of an amorphous substance

and nuclear fragments. In some places this material took a bright red eosin stain. At the periphery of the larger caseous areas the lung tissue was col-

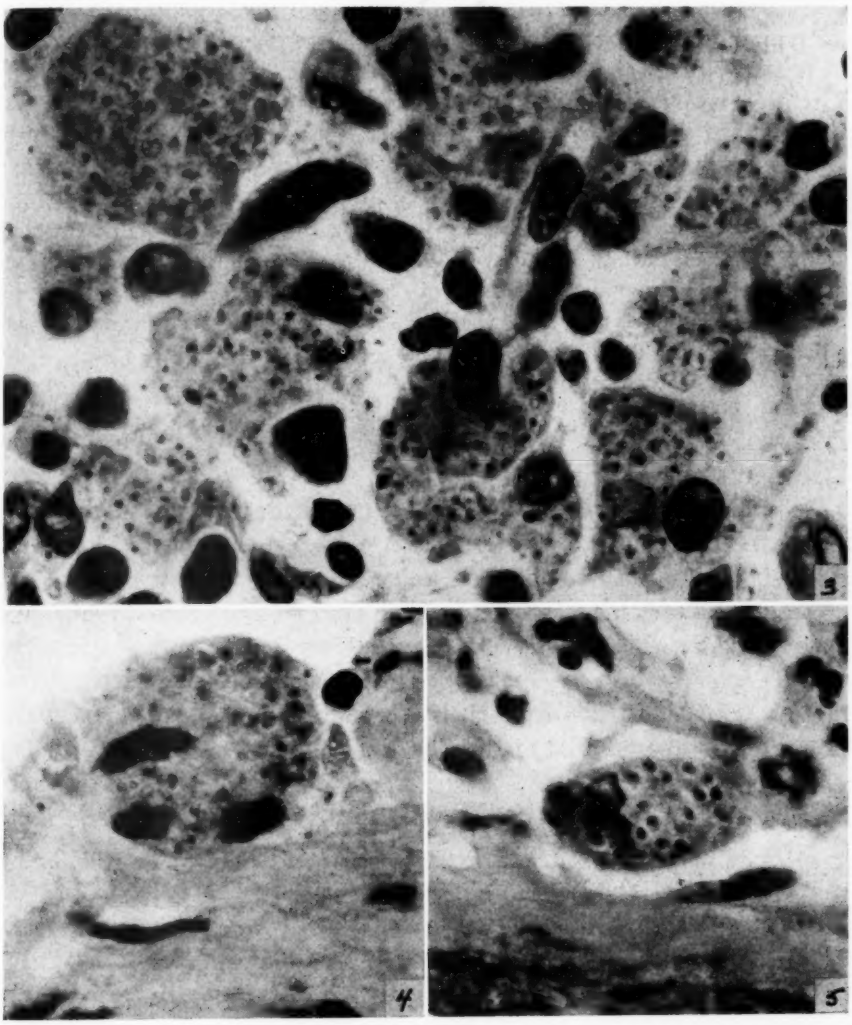

FIG. 3. Case 1. Macrophages containing *Histoplasma capsulatum* in alveoli of lung. × 800
FIG. 4. Case 2. Edge of abscess cavity. Partly degenerated parasites in large mononuclear phagocyte having three nuclei. × 800
FIG. 5. Case 2. Parasitized macrophage in edge of granulation tissue lining a cavity. × 800

lapsed, and in the remains of the alveoli and in the interstitial tissue were many large mononuclear phagocytes containing innumerable parasites and a few

particles of carbon pigment (figure 3). A few giant cells were present at the periphery of these nodules. Some of the lymphatic vessels in the neighborhood of these areas contained many parasitized macrophages. Some of the smaller caseous nodules showed no parasitized cells at the periphery but did not have the typical epithelioid structure of tubercles. In some of the smaller caseous areas Ziehl-Neelsen stain showed a few acid-fast bacilli having the morphology of tubercle bacilli.

Sections of the liver showed considerable degeneration, fat infiltration and haemosiderin pigment in the cells at the centres of lobules. Scattered through the tissue were a number of small caseous areas similar to those in the lungs. No parasitized cells were found in association with these nodules or elsewhere in the liver. Acid-fast bacilli were found in some of these nodules. The spleen showed similar caseous areas but no parasitized cells. Acid-fast bacilli were found in some of the caseous areas. Neither caseous areas nor parasitized cells were found in the other organs of the body.

Comment: It seems apparent that the disease in the lungs was caused chiefly by *Histoplasma capsulatum*. In previously reported cases the characteristic localized lesion consists of a caseous necrosis surrounded by a marked infiltration of macrophages filled with parasites. The most striking feature of the lesions in this case within the lung parenchyma is the invasion of these cells into the alveoli surrounding the necrotic areas. Some of these areas had apparently involved the pleura and produced the extensive necrotic exudate on its surface. The smaller caseous areas both in the lungs and in the liver and spleen were structurally indistinguishable from the larger areas in the lungs which were surrounded by parasitized macrophages. They did not have the typical structure of tubercles. The finding of acid-fast bacilli in these lesions, however, seems to indicate that they were caused by the tubercle bacillus. The presence of calcified areas in the lungs is indicative of a previous tuberculous infection and it seems probable that the lowered resistance of the patient was responsible for both the lighting up of a silent tuberculous infection and the development of the histoplasma lesions from parasites already present in the respiratory tract.

Case 2: G. S. H., Vanderbilt University Hospital No. 99061, white male, age fifty, a restaurant operator in a small town in Middle Tennessee, was admitted on May 19, 1939, with a diagnosis of urinary calculus with ascending renal infection. A calcium stone the size of a hen's egg was discovered in the bladder. The patient had had pneumonia in 1936. Since that time he had had night sweats which he referred to his urinary condition. He had lost 16 pounds in

weight during the past six months. Physical examination showed the patient to be considerably emaciated. Aside from the evidence of ascending renal infection, he had physical signs of cavities at the apices of both lungs and moist râles over both bases posteriorly. X-ray examination of the chest revealed a large cavity at the left apex and a smaller one on the right with exudation in the parenchyma of both upper lobes (figure 2). The patient's temperature was normal. His blood showed 4,000,000 red blood cells with 12.2 g. of haemoglobin and 13,800 white blood cells with 65 per cent neutrophiles. His urine contained pus and blood. The Kahn reaction was negative. The nonprotein nitrogen was 35 mg. per cent. The sputum was repeatedly examined and on two occasions acid-fast bacilli were found. Cultures of the sputum yielded *Staphylococcus aureus* and haemolytic streptococcus. After six days of observation a cystostomy was performed, the bladder stone removed, and a catheter inserted for irrigation. The patient did poorly after the operation. He developed bloody diarrhoea, a persistent cough with blood tinged sputum, paralytic ileus and died on June 1.

Autopsy showed a fibrinous peritonitis, ascending renal infection with hydronephrosis of the right kidney and pyelonephritis of the left. A small gastric ulcer was present and the caecum and ascending colon contained numerous irregular shallow ulcers. The heart and blood vessels were normal. The pleural cavities were dry but the apices of both lungs were firmly adherent to the parietal pleura. In separating these adhesions several cavities in both lungs were ruptured, liberating yellow purulent fluid. The cavities measured from 0.5 to 2 cm. in diameter and were surrounded by a thick wall of grayish fibrous tissue about 1 cm. in thickness. The remaining portions of the lungs were normal in appearance except for congestion. The bronchial lymph nodes were slightly enlarged and filled with carbon pigment but showed no evidence of tubercle formation. The other organs were essentially normal.

Microscopical sections from the lungs showed the walls of the cavities to consist of granulation tissue undergoing degeneration into caseous material containing nuclear fragments. Where degeneration was not complete there were numerous lymphocytes, monocytes, plasma cells and a few polymorphonuclear leucocytes. In the edges of the cavities there were occasional macrophages, some of a very large size, filled with parasites morphologically similar to *Histoplasma capsulatum*. In some of these cells the parasites appeared to be degenerated showing pale-staining nuclear material with little evidence of a capsule (figure 4). In other cells the parasites were normal in appearance (figure 5). The pleural surfaces adjacent to the abscesses showed similar development of granulation tissue and caseous necrosis with a few parasitized macrophages. An occasional giant cell was present in the granulation tissue. Smears and sections stained with Ziehl-Neelsen stain failed to reveal any acid-fast bacilli. Neither was there any evidence of tubercle formation in the

lungs or in other organs of the body. The bronchial lymph nodes showed carbon pigment and dilated lymph sinuses but no parasites. Sections from the stomach and colon showed shallow ulcers with fibrinous exudate. The ulcers in the colon appeared to be pyogenic in origin. No parasites were found. Except for the lesions in the urinary tract, the other organs were essentially normal.

Comment: This case, from the point of view of the lungs, was diagnosed tuberculosis by physical examination, X-ray and the finding of acid-fast bacilli in the sputum. In view of these findings it is probable that the primary infection was tuberculosis. The finding of histoplasma-like organisms in the edges of the cavities suggests, however, that this infection was at least partly responsible for the terminal development of activity in this tissue.

DISCUSSION

These cases are presented as one form of infection by *Histoplasma capsulatum.* In the cases described this fungus was responsible for a terminal infection but it is probable that in some cases it may initiate severe pulmonary lesions. It is believed that when this infection becomes more generally recognized it will be found frequently at autopsy and that familiarity with the condition will lead to the diagnosis of many cases before death.

One interesting feature of the cases so far described is that most of them have lived in small towns or rural areas. The source of the infection has thus far not been discovered. The fungus has not been found free in nature but the production of hyphae in cultures indicates that under favorable conditions it may multiply outside the animal body. Its discovery in lower animals and the fact that it sometimes produces lung infections suggest that it may sometimes be transmitted from one warm-blooded host to another.

SUMMARY

Two cases of histoplasmosis of the lung discovered on microscopical examination of autopsy material are described. Although in one case acid-fast bacilli were found in caseous lesions in the lungs, liver and spleen and in the other case a diagnosis of chronic pulmonary tuberculosis with cavitation was made clinically, the evidence suggests that *Histoplasma capsulatum* was responsible for the terminal activity of the pul-

monary lesions of both cases. It is probable that this infection is much commoner than the number of reported cases indicates.

The author is indebted to Dr. E. W. Goodpasture, Dr. G. J. Buddingh and Dr. W. J. Cromartie of the Department of Pathology, Vanderbilt University School of Medicine, for permission to publish these cases and for the preparation of the photomicrographs.

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Allen Kramer Krause

1881–1941

Dr. Allen Kramer Krause died May 12, 1941 in Providence, Rhode Island, following several years of illness.

He was born in Lebanon, Pennsylvania on February 13, 1881. He graduated from Brown University in 1901 and received his A.M. from this University in 1902. He studied medicine at Johns Hopkins University where he received his M.D. in 1907, when he was appointed Instructor in Pathology. Following a brief episode of active tuberculosis, for which he sought treatment in Saranac Lake, he became Assistant Director of the Saranac Laboratory, which position he held until 1916. In 1914 he underwent an operation for carcinoma which fortunately proved to be permanently successful. In 1916 he was appointed Associate Professor of Medicine at Johns Hopkins University, Director of the Kenneth Dows Tuberculosis Research Laboratories and Associate Physician, Johns Hopkins Hospital and Physician in Charge of the Phipps Tuberculosis Dispensary. In 1929 he left Johns Hopkins University to become President and Director of The Desert Sanatorium in Tucson, Arizona, which positions he held until 1937. When he left Baltimore, Johns Hopkins University made him Visiting Lecturer in Medicine. Stanford University appointed him Clinical Professor of Medicine in 1929 and three years later the University of Southern California conferred the same honor upon him.

He was Managing Editor of the American Review of Tuberculosis during its first five years, from 1917 to 1922, and then became Editor. He was the Editor of the American Section of Tubercle, and he was on the Editorial Board of several distinguished foreign magazines. He belonged to a number of scientific and medical societies, and was elected honorary member of the Harvey Society, of the Interurban Clinical Club, of the American Society for Clinical Investigation and of the Los Angeles Clinical Pathological Society.

Among his more than two hundred publications on various aspects of tuberculosis are a number of contributions in reference works and textbooks, such as the Encyclopedia Britannica, Nelson's Loose Leaf System

Allen Kramer Krause
1881–1941

of Medicine, Osler's Modern Medicine, Cecil's Text-Book of Medicine and Piersol's Cyclopedia of Medicine.

In 1931 he was awarded the Trudeau Medal by the National Tuberculosis Association. He was one of the "starred men" in American Men of Science.

In 1906 he married Clara Fletcher of Providence, Rhode Island, whose loyalty to him did much to ease the burden of his last difficult years. They had three sons.

In his scientific writing, Allen Krause always showed his clear discrimination between the essential and the incidental. Starting with his early work in Saranac Lake he recognized the importance of allergy, immunity and their manifestations, and this general subject remained one centre of his interest even after he had stopped contributing to it. Building on the foundation of the experimental work by Koch, Trudeau and Röhmer, he elaborated and clarified the complex relations between immunological factors in the widest sense of the word and the clinical manifestations of disease. In well planned and painstaking series of experiments he traced the causal and quantitative relation between immunity, anaphylaxis and allergy. He recognized the dependence of systemic symptoms and caseating processes on the development of allergy which in turn he related correctly to the formation of specific tissue. In logical sequence these ideas were later elaborated and followed in their ramifications by Allen Krause and his coworkers in the Kenneth Dows Tuberculosis Research Laboratories in Baltimore.

He was keenly interested in the clinical application of his experimental work, particularly in regard to tuberculosis in children. He was among the first authors who observed the waning of tuberculin allergy in patients who had had active tuberculosis.

With his analytical mind he studied the broad aspects of epidemiology and the relation of tuberculosis to Public Health and the changing socio-economic conditions.

His profound knowledge of the history of medicine found expression in numerous speeches of absorbing interest, but unfortunately no written record of these is extant.

When in later years significant papers appeared that seemed to refute some of his fundamental conclusions, he refrained from public rebuttals, although in private remarks he indicated precisely the vulnerable points in the arguments of his scientific adversaries. He rarely found much fault with work done: his criticism was usually directed against some

"loose reasoning" in comments and generalizations. When asked to defend his own conclusions against contrary opinion, he always refused. He felt that the record of his work was there for future workers to examine and that a definitive decision would not be made by one participant in the dispute. But there was hardly a doubt in his mind as to what the final decision would be.

A true evaluation of Allen Krause as physician and scientist is impossible on the basis of his writings and speeches alone, even if the latter had all been preserved, which is not the case for many excellent ones. There is hardly another man of his generation who has done so much to awaken interest in tuberculosis, both in the profession and in the lay public. In innumerable speeches in many parts of this country he created that mental attitude that led to research and practical application of his teaching. To evaluate truly, one would have to know, furthermore, the immeasurable influence of his verbal teaching, in classrooms, in casual discussions in small groups or just from man to man; and of great importance would be the knowledge of his voluminous correspondence. He was a facile and devoted letter-writer, though letters might not always come when expected; he was fast in dictating long letters—and some of his most elaborate letters never were sent off. In his sensitiveness he frequently refrained from delivering the criticizing or even damning blow that appeared justified by his reasoning; and, on the other hand, he had found out that "many letters take care of themselves, if you just keep them long enough on your desk."

Allen Krause was Editor of the American Review of Tuberculosis for twenty-three years. He is almost single-handedly responsible for the high standards and the enviable reputation of the Review. His editorial work was most painstaking and every tiny detail seemed sufficiently significant to him to give it his full attention. The correspondence files of the Review are a testimony to the wide and fertile influence that he exerted on many contributors. He would not hesitate to return for adequate reasons a manuscript to an author well established in position and reputation; but the young and unknown author would get his full attention and consideration, his advice for alterations and further work and always his encouragement.

In these functions as scientist, teacher, speaker and editor his influence on the tuberculosis work in this country was immense, in regard to basic concepts, scientific stimulation and diffusion of knowledge. It must be realized that his influence went far beyond the effects of his own scien-

tific work. This is so not only on account of the more hidden sources of influence, such as private conversation and correspondence, but, in my opinion, because Allen Krause was a master in speaking and writing. He never wrote a dull paper, he never wrote one whose style was not lucid and beautiful. And he had one great and rare art: he always sensed correctly the mental level of his audiences; he never spoke down to them, nor "over their heads." It certainly is profoundly true that tuberculosis work, here and now, would be a much poorer thing without Allen Krause.

The mental process that had ever the greatest fascination for Allen Krause, and one in which he was master, is what we may call imaginative correlation. For this he was equipped with an astounding store of factual knowledge to which he had ready access through a trigger-like mechanism of selective memory. This facile process was controlled by a high accuracy of mental vision and a profound sense for the propriety and significance of associations. Conversely he had but faint praise for knowledge *per se*, if it was not enlivened by a sense of proportion and if it was limited to one field. What he valued was "the type of mental process," "how a person can think." He found the expression "the most learned fool in Christendom" rather often applicable. His Hermann M. Biggs Memorial Lecture on Public Health and Tuberculosis is an excellent example of his ability to marshal most diverse facts and to assemble them into a purposive unit.

One cannot draw a line between his work and his hobbies. His deep interest in and far more than amateurish knowledge of literature, history and music are reflected in many of his scientific writings, they pervade his teaching and speaking and they are part and parcel of the fulness of his human personality.

And Allen Krause the man? It is with great hesitation that I try to formulate my impressions because I know that many readers of this, who have known Allen Krause, could not agree among themselves. And I, too, have known many different Allen Krauses. And so, some might conclude that his outstanding characteristic was inconsistency. He was as much more inconsistent than the average man, as the organ is more "inconsistent" than the spinet. The multiplicity of registers, the wide differences in pitch, the range of tonal qualities and quantities of the organ make for infinite diversity, but the instrument remains one functional unit. And so it was with Allen Krause; he had at his command a much greater variety of registers in action and expression than is usually given to man. And only by long and close acquaintance did one

find that they all added up to one organic unit with all its dissonances and with all its harmonies. He was neither optimist nor pessimist, he was both. He had the objectivity of the scientific mind and the imaginative dream of the utopian. He had the humility of religious acceptance and the force of realistic self-assertion. He had the gentle sensitivity of the artist and the robust will-power of the business man. He could see his ego as an insignificant atom and he could see himself as the centre of the stage. So he combined thesis and antithesis of human thoughts, volitions and emotions. But out of the almost chaotic riches of his personality he had built his own life, his own world, with determined opinions in science, philosophy and art. And he had the will-power and the moral strength to live in his world and to defend it against whatever onslaughts realities might make.

In kindness and sternness he had a great personal charm. Of all the many hundred people who walked in and out of his office, there were few who did not leave richer and happier than they entered—and none could easily forget the man. His work and a host of profoundly devoted friends are living monuments to his greatness.

MAX PINNER

DEMONSTRATION OF TUBERCLE BACILLI BY FLUORESCENCE MICROSCOPY

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Fluorescence is a property of certain substances whereby the absorption of invisible, ultraviolet radiation stimulates the emission of visible light. Exactly how this takes place is not clearly known but it presumably involves electronic rearrangement. Since acid-fast organisms will absorb and retain certain fluorescent acid-fast materials in the same manner that they retain acid-fast dyes the principle affords a new approach to the problem of demonstrating acid-fast organisms. In practice it appears to have certain advantages over other methods.

HISTORICAL

The spontaneous fluorescence of some substances was observed by Köhler (1904) while experimenting with the ultraviolet darkfield microscope. The fluorescence microscope appeared in Europe from 1911 to 1913, although little serious work was done at that time. Provazek (1914) discovered that substances which did not fluoresce spontaneously could be made to fluoresce by soaking them in a fluorescent chemical.

The spontaneous whitish-blue fluorescence of a suspension of human tubercle bacilli was observed by Kaiserling (1917). A bovine strain was greenish. Detailed spectroscopic observations were made. Later (1921) he published observations on other bacteria with a color intensity rating scale. Arloing, Policard and Langeren (1925) noticed that the spontaneous fluorescence of human tubercle bacilli was gray, while a bovine strain fluoresced violet. Barnard and Welch (1936) have reported that the bacterial cell membrane did not fluoresce, but some of the cellular content did.

In 1937 Hagemann observed the fluorescence of virus, tubercle and leprosy bacilli after staining in berberine sulfate in phenol and decolorizing with acid alcohol. This initiated the fluorescence technique for the identification of acid-fast bacteria. Hagemann (1938) found auramin superior to the berberine for tubercle bacilli. This method was con-

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firmed by Keller (1938) who also found the dye, coriophosphine-H, suitable for the fluorescent observation of diphtheria bacilli. The diphtheria bacilli fluoresced green with a brick red granule while the pseudodiphtheria bacilli fluoresced a pale yellow. Low voltage, high amperage filament bulbs were found by Keller to give sufficient ultraviolet rays when used with proper filters. Simple fluorescence equipment then became practical and a description of the equipment manufactured by Reichert is given in Keller's paper.

The advantages of the fluorescence method were reported by Hermann (1939) who stated that he found more positive sputa with the fluorescence technique than with the Ziehl-Neelsen stain. Küster (1939) reported that the fluorescence method was good for tuberculosis and leprosy bacilli, but not generally useful for acid-fast bacteria. The superiority of the fluorescence technique as compared to the usual staining methods was confirmed by Clauberg and by Didion in 1939. Kline and Leach (1940) reported the fluorescence technique suitable for demonstrating tubercle bacilli, lepra bacilli and nonpathogenic acid-fast organisms. The general field of fluorescence microscopy is reviewed by Ellinger (1940).

APPARATUS

For the demonstration of acid-fast organisms a simple fluorescence apparatus for use with monocular microscopes has been designed by one of us (O. W. R.). It consists essentially of light from a source rich in ultraviolet rays passed through a blue ultraviolet transmitting filter, reflected through the microscope from an aluminum surfaced mirror and finally passed through a yellow contrast filter placed in the eye-piece.

The high amperage, low voltage, concentrated filament bulb is satisfactory for this purpose. Filters are chosen so that the ultraviolet radiation and blue light transmitted by the lamp filter are absorbed by the yellow eye-piece filter and the field appears dark. Bacteria retaining auramin after staining appear as self-luminous, golden yellow, bodies with a distinctive morphology. They appear somewhat similar to darkfield preparations although the two methods have no relation to each other. The contrast between the organisms and the background is so great that the bacteria are easily recognized at comparatively low magnifications. The organisms can be located on a slide with a 16 mm. objective and the 20× compensating eye-piece. They can be seen in sufficient detail to be recognizable with the 8 mm. objective and the 20× compensating

eye-piece or with a 4 mm. objective and a 10× eye-piece. If the 4 mm. objective is used somewhat better results can be obtained by one of N.A. 0.85 than by one of N.A. 0.66 which transmits only about 60 per cent as much light.

The permanent glass filters used are of American manufacture and have been chosen to give better contrast than the European filters. The blue filter transmits ultraviolet, violet and a small amount of blue rays. The yellow filter transmits no blue light. The yellow light emitted by the auramin stained tubercle bacilli is approximately of wave lengths 0.520 to 0.650 μ. This choice of filters, as well as the choice of the filament bulb type of illumination, simplifies the method but restricts it to use with materials whose fluorescence will be excited by the available ultraviolet and which may be seen through the yellow filter. It is not adapted to all types of fluorescence microscopy. The yellow filter used in the eye-piece prevents ultraviolet radiation from interfering with the visual picture and protects the observer's eyes from damage which might result from ultraviolet radiation.

PROCEDURE

1: Make direct smears of sputum or of sputum concentrate on glass slides and fix by heat in the usual manner.
2: Stain for two to three minutes with a solution of 0.3 per cent auramin in 3 per cent carbolic acid solution at room temperature.
3: Wash with water.
4: Decolorize with a solution of 0.5 per cent concentrated hydrochloric acid and 0.5 per cent sodium chloride in 70 per cent alcohol for one minute, pour off and add fresh decolorizer for two additional minutes.
5: Rinse, dry and examine.

Smears should preferably be made with fresh sputum. If a preservative is desirable, phenol will be more satisfactory than cresol which reduces the number of organisms and causes an interfering fluorescence. Autoclaving will greatly reduce the number of organisms seen.

This staining technique is not a painstaking or critical one. Almost any concentration of auramin will give the desired result, as little as 0.05 per cent of dye may be used. The concentration of phenol may also be reduced. Satisfactory results have been obtained with 0.5 per cent auramin in 2 per cent phenol. The stain originally recommended was 0.1 per cent auramin in 5 per cent phenol. The auramin is dissolved with gentle heat but the stain becomes cloudy on cooling. Cloudy solutions

are just as satisfactory as clear ones, but should be shaken just before using. The stain, after a number of weeks, gradually loses some of its fluorescent properties. Smears of known positive sputa should be stained and examined occasionally as a check on the keeping qualities of the dye.

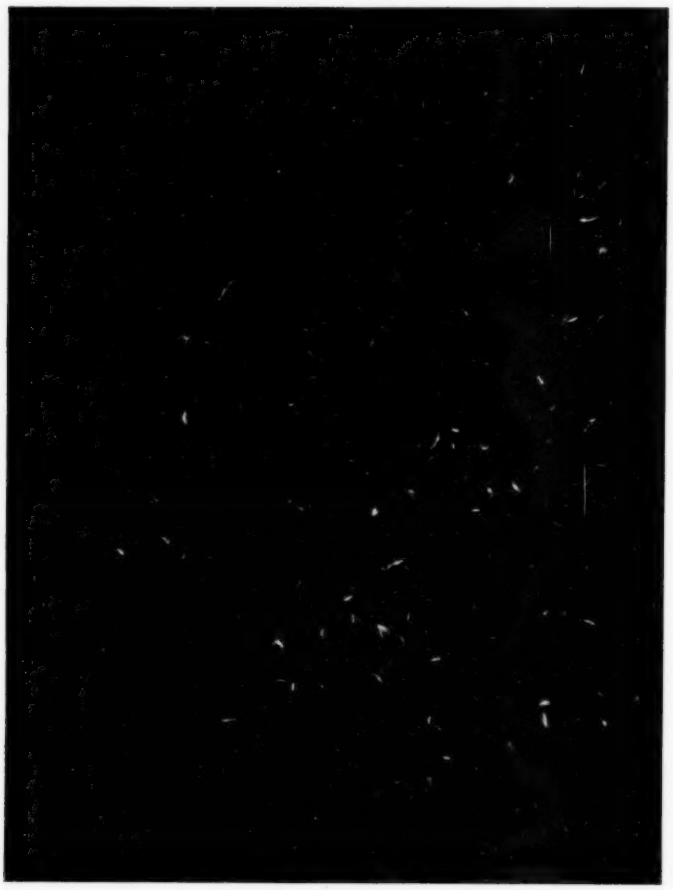

FIG. 1. Photomicrograph showing tubercle bacilli in a sputum smear (Magnification ×400)

Almost any of the standard decolorizing agents mentioned for decolorizing tubercle bacilli, such as 3 per cent hydrochloric, 5 per cent nitric, or even 25 per cent sulphuric acid, may be used. These stronger reagents require more careful timing, most of them decolorize in from twenty to thirty seconds. The slower decolorizer, with a three minute period, is recommended.

If the source of light is strong enough it is possible to check positive findings by use of an oil immersion lens with oil of sandalwood (cedar oil is fluorescent). In this case the field appears gray rather than black but the organisms can readily be identified. After a little practice an operator becomes satisfied that the high dry images are reliable and rarely resorts to oil immersion checks. (See figure 1.)

EXPERIMENTAL

Hermann stated that he found from 6 per cent to 17 per cent more positive sputa with fluorescence technique than with Ziehl-Neelsen's stain (1939). Clauberg (1939) found 18 per cent more positives with fluorescence than with Ziehl-Neelsen's and Didion (1939) states that the number of organisms counted per minute in a test run was 48 for fluorescence and 13.2 for Ziehl-Neelsen. Our own experience indicates that more bacilli are found in sputum smears from known cases of tuberculosis by fluorescence methods than by Ziehl-Neelsen stain. This has also been true of a number of positive sputa diluted 1:100 and examined by both methods and of sputa concentrates prepared by the chemical flocculation method of Hanks, Clark and Feldman (1938).

Table 1 shows comparative numbers of organisms seen by the two methods in a series of tests selected at random from our experience. The first two columns represent numbers of organisms seen per 100 fields examined and thus may be said to represent numbers seen by an equivalent amount of microscopical work, although as a matter of fact the organisms are much easier to see and enumerate on the fluorescent preparations because of the greater contrast between organism and background. Since different optical systems are used in the two methods there is a considerable difference in the area of the slide covered by 100 fields. To better compare the numbers demonstrated the third column of table 1 represents the ratio of numbers of organisms seen on equal areas of the duplicate slides. It will be noted that there is little uniformity in this ratio. A comparison of all the slides on which we have made parallel counts shows that the number of organisms seen by fluorescence technique averaged 3.65 times the number seen by Ziehl-Neelsen stain in equal areas of duplicate preparations.

It has not been possible for us to devise a staining technique whereby organisms could be rendered visible in the same preparation by both methods. It is possible, however, to apply Ziehl-Neelsen stain to a smear which has been previously stained and examined by fluorescence technique. Experimental studies of smears partially stained by this double

method and partially stained by Ziehl-Neelsen stain alone have indicated that there is no diminution of the number of organisms stainable by Ziehl-Neelsen as a result of previously staining with auramin. Several series of examinations have been made on ruled slides in which it is possible to examine exactly the same microscopical field by the two methods, staining and examining first with carbol-auramin and later with Ziehl-Neelsen. In general, it would seem that a greater number of organisms are stained by auramin and demonstrated by fluorescence than are stained by Ziehl-Neelsen. However, occasionally a single organism has been stained by

TABLE 1

Number of acid-fast organisms seen in duplicate sputa smears

DIRECT SMEARS OF SPUTA			CHEMICAL FLOCCULATION CONCENTRATES			DILUTED SPUTA		
Z-N	Fl	R	Z-N	Fl	R	Z-N	Fl	R
780	6,800	187	150	1,020	146	46	760	355
300	3,800	271	24	1,060	869	20	188	202
200	4,200	450	16	200	267	5	500	2,174
165	4,100	532	10	120	261	4	92	484
150	1,100	157	7	150	455	2	80	889
15	110	157	5	50	217	1	100	2,000
10	20	43	3	42	300	1	32	640
7	400	1,212	2	42	467	1	16	320
0	128		1	62	1,240	0	18	
0	106		1	18	360	0	12	
0	64		0	14		0	10	
0	5		0	12		0	7	

Z-N = Organisms seen in 100 fields stained by Ziehl-Neelsen. Area of field 1.5 sq. mm.
Fl = Organisms seen in 100 fields stained by fluorescence technique. Area of field 7.0 sq. mm.
R = Ratio between equal areas expressed as the number of organisms seen on Fl per each 100 seen on Z-N preparations.

Ziehl-Neelsen which had not been demonstrated by fluorescence. Figure 2 illustrates the findings by this method. Each figure represents four microscopical oil immersion fields centred around a set of ruled cross lines placed on a glass slide. More organisms are seen in the fluorescence stained preparation, but organisms marked "X" appear only in the Ziehl-Neelsen stained slide. The smaller figures represent quadrants of high and low ratio sputa. All of these figures are drawn from oil immersion fields representing equal areas.

It is evident from these experiments that neither method will stain all

acid-fast bacteria; however, there does seem to be a definite superiority to the fluorescence results. Some experiments with mycolic acid, the acid-fast component of tubercle bacilli, indicate that this substance stains more intensely with carbol-auramin than with carbol-fuchsin and also

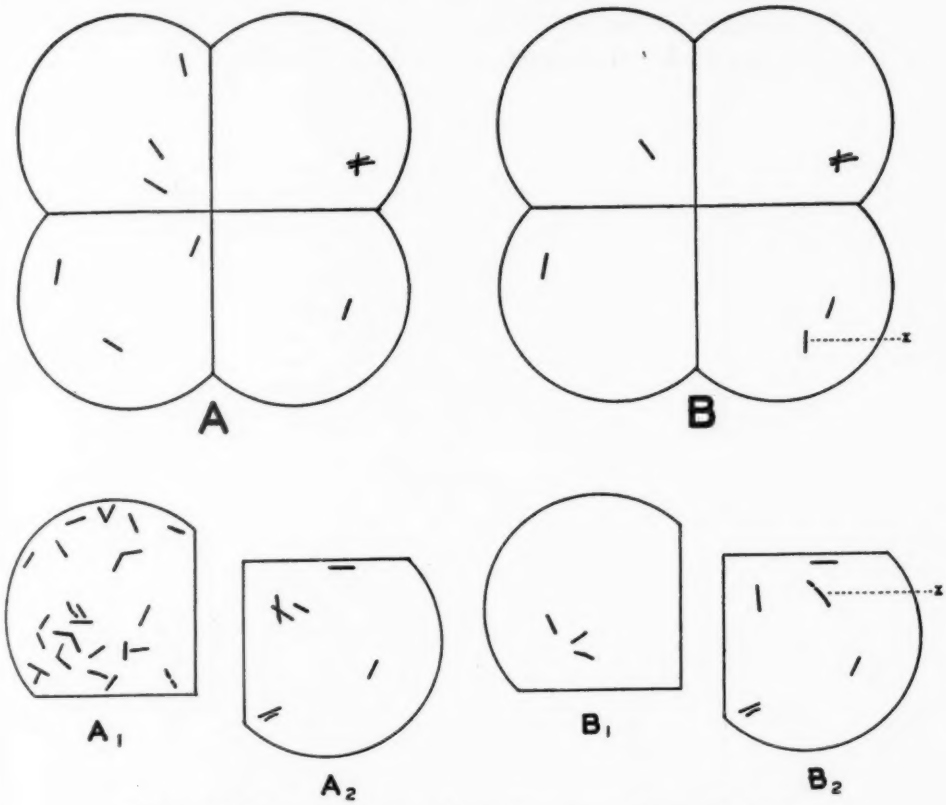

FIG. 2. Acid-fast organisms appearing on the same portions of ruled slides

A: A sputum smear stained and examined by fluorescence technique.
B: The same smear stained and examined by Ziehl-Neelsen technique.
A_1 and B_1: Fluorescence and Ziehl-Neelsen stains of a high ratio sputum.
A_2 and B_2: Fluorescence and Ziehl-Neelsen stains of a low ratio sputum.
X: Organisms appearing on Ziehl-Neelsen and not on fluorescence stain.

resists destaining for a longer time (Richards, 1941). This may account for some of the observed differences.

Several series of experiments were performed with diluted sputa on which the following is illustrative of the results uniformly obtained. A specimen of sputum from a known case of tuberculosis showing a single

bacillus in many fields was thoroughly emulsified by shaking in a mechanical shaker with glass beads, then diluted with distilled water to which had been added about 1 per cent of egg albumin. Ten cc. of each of several dilutions were prepared, direct smears made for staining by each method, after which each dilution was concentrated by chemical flocculation concentration method. Smears were prepared in duplicate from the sediments of the concentrates and stained by both methods. Table

TABLE 2

Acid-fast bacilli in diluted sputa

VOLUMES TO WHICH ONE VOLUME OF SPUTUM WAS DILUTED	NUMBER OF ORGANISMS COUNTED IN 100 FIELDS			
	Ziehl-Neelsen stain		Fluorescence technique	
	Direct smears	Concentrations	Direct smears	Concentrations
1	7	30	400	700
2	5	16	500	300
4	2	7	200	150
6	1	6	100	110
8	1	10	32	120
10	1	4	18	100
12	1	5	16	50
14	0	3	12	42
16	0	2	10	52
18	0	1	18	62
20	0	2	14	42
25	0	1	5	28
30	0	1	6	24
40	0	1	3	26
60	0	0	2	12
80	0	0	2	14
120	0	0	0	6
160	0	0	0	1
200	0	0	0	+

Areas of fields same as in table 1.

2 shows the number of organisms per 100 fields by each method. It will be noted that not only were larger numbers of organisms seen by the fluorescence method but also that organisms appeared in higher dilutions.

The most striking difference between fluorescence examinations and Ziehl-Neelsen examinations lies in the greater contrast between the organisms and the field which is obtained in the former method. Acid-fast bacilli examined under fluorescence stand out so that they are readily recognized with a minimum of adjustment of the eye from field to field

so that not only is the method preferable because a larger field is examined but also because the experienced operator spends much less time in examining a single field than is the case with Ziehl-Neelsen stains. Even after considerable experience with the latter, one must search a field rather carefully in order not to overlook acid-fast organisms. This is particularly true in smears which are reasonably thick.

ROUTINE APPLICATION

Richards and Miller (1941) report the first use of the equipment in the routine examination of sputa. They examined 100 specimens and obtained 11 which were negative by Ziehl-Neelsen stain on direct smear and positive by fluorescence technique. Of these, 6 were positive by Ziehl-Neelsen stain after concentrating by the Petroff method. They also report demonstration of acid-fast bacilli by fluorescence technique after failure to demonstrate them by Ziehl-Neelsen stain in a specimen of spinal fluid from tuberculous meningitis and in pus.

The Cattaraugus County Laboratory has used the method in parallel with Ziehl-Neelsen stains on both direct smears and concentration tests on all sputa received over a four-month period. In all, 324 specimens were received. After subtracting 87 positive by both direct smears, which were not concentrated, as well as 73 that were of insufficient quantity to furnish satisfactory concentration tests, there remained a total of 164 on which all four tests were performed. Of these, 134 were negative by all methods, 14 positive by all methods, except Ziehl-Neelsen direct smear, 7 were positive by both fluorescence direct smear and concentrate and negative by both Ziehl-Neelsen examinations, 1 was positive by both concentration tests and negative on both direct smears, and 8 were positive by fluorescence concentration only.

If we consider all specimens which were positive by any method as being the total number of positives in our series and assume that direct-smear positives would yield positive concentration tests in those positive specimens which were not concentrated, we find that fluorescence examinations of concentrates yielded 100 per cent positives, fluorescence examinations of direct smear 92.3 per cent, Ziehl-Neelsen examination of concentrates 87.0 per cent and Ziehl-Neelsen examination of direct smears only 74.3 per cent.

Particular interest is attached to the 15 specimens in this series which were negative by Ziehl-Neelsen stains and positive by fluorescence methods. They were obtained from 10 patients on whom a diagnosis of

pulmonary tuberculosis had previously been made. Four of them furnished sputum positive by both fluorescence direct smear and concentrate methods, and 6 had sputum positive by fluorescence concentration only. One patient had 3 specimens taken at monthly intervals, 3 patients had 2 positive specimens taken on different days, and the remaining 6 had only one positive specimen.

A consideration of these findings in relation to the problem of the classification[3] of the patients according to the Diagnostic Standards of the National Tuberculosis Association (1940) shows that all except 2 patients were classified as being in the active stage of the disease. One of these 2 patients would have been transferred from "apparently arrested" to "arrested" without fluorescence examinations. The other, although classified as arrested, apparently had an unstable lesion in which this examination indicated activity earlier than it was apparent by either Ziehl-Neelsen stains or clinical observation. Six weeks after this positive fluorescence examination, this patient showed a Gaffky I finding on direct smear by Ziehl-Neelsen staining and subsequently 5 positive Gaffky I and Gaffky II smears were obtained.

On the whole the requirement that sputum shall be concentrated and examined (by Ziehl-Neelsen, the method available at the time Diagnostic Standards were written) before being called negative is met and indeed slightly surpassed by substituting direct fluorescence examinations for concentration and examination by Ziehl-Neelsen stain. In the entire routine series 31.3 per cent of the specimens were positive by Ziehl-Neelsen concentration and 33.3 per cent by direct fluorescence examination.

Concentration and examination by fluorescence offers a more delicate test than has heretofore been available and it is recommended that at least for the present it be reserved for investigational work. It should not be substituted for the present accepted, less sensitive methods, in the clinical evaluation and classification of patients until further information is obtained as to the clinical significance of such findings.

CONCLUSIONS

The newly designed equipment for fluorescence demonstration of acid-fast organisms has the following advantages over older methods for examining smears of sputum and other material for the presence of tubercle bacilli:

[3] Classification data furnished by Dr. E. K. Richard, Director, Bureau of Tuberculosis, Cattaraugus County Department of Health.

(*a*) The method stains more acid-fast bacteria than are stained by the Ziehl-Neelsen technique.
(*b*) Examinations can be made with high dry objectives covering fields which are larger than oil immersion fields as well as being simple and more convenient for use.
(*c*) A greater contrast obtains between the stained organism and other material present on the slide.

In experimentally diluted sputa and in a series of 324 routine specimens, fluorescence examinations of direct smears yielded slightly better results than Ziehl-Neelsen examination of concentrated specimens.

A certain number of positive findings occurred among specimens which were negative by Ziehl-Neelsen stained direct smears and concentration tests, 4.6 per cent of the routine series.

Correlation of these findings with clinical evidence indicated that in no case were the findings by fluorescence technique incompatible with clinical status.

Because of the great saving in the amount of labor involved it is suggested that routine laboratories may well adopt fluorescence examinations of direct smears in place of concentration and staining by Ziehl-Neelsen.

Concentration and examination by fluorescence technique is a more sensitive method than has heretofore been used and may well be reserved for special investigations until further studies have been made of the correlation between clinical status and fluorescence findings.

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DETECTION OF TUBERCLE BACILLI BY FLUORESCENCE MICROSCOPY[1,2]

EMIL BOGEN

The fluorescence method for the detection of tubercle bacilli was introduced by Hagemann (7, 8) in 1937. More than a dozen reports from different parts of Germany (1, 2, 4, 5, 6, 10, 11, 12, 14, 19, 20, 22), Italy (3), Holland (17), Scandinavia (13) and America (15, 18) attest its superiority both in speed and delicacy. Improvements in the technique have been introduced by several workers, and others are being tried at the present time.

Ordinary microscopical visualization of bacteria depends upon the obstruction offered to the transmission of certain light rays by the stained or unstained organism. If the obstructing body is too small, the area of diminution or change cannot be distinguished from the remaining illuminated field, and so the organism is not seen. This definitely limits the possibilities of detection of minute forms by transmission microscopy.

Fluorescence microscopy depends upon the ability of certain substances to transform incident radiation into emergent waves of lower frequency. These longer waves in the region of the visible spectrum may be seen when other visible light is excluded by suitable filters. The points of light may be seen, however small, and visualization of minute forms with relatively low magnification is therefore possible.

Nonfluorescent structures, such as bacteria, may be made to fluoresce by impregnation with strongly fluorescent chemicals, such as certain dyes. Fluorescent staining results in the bacteria emitting light of a wave-length that will pass the eye filter, and so be seen in a field in which all other such light has been excluded. After impregnation with the diphenyl-methane dye, auramine, tubercle bacilli retain the fluorescent stain despite treatment with acid alcohol which removed it from non-acid-fast materials. They may, then, be seen through a fluorescence microscope.

[1] From Olive View Sanatorium, Olive View, California.

[2] With the aid of Work Projects Administration, Project No. 665-07-3-223, Los Angeles County, California.

Fluorescence microscopy may use a special source of light which gives intense illumination of short-wave length, such as that generated by an electric arc or a quartz lamp. Visible violet and longer ultraviolet waves which will pass through ordinary glass are, however, able to excite fluorescence with auramine. A simpler mercury vapor lamp (16) or even a high-powered filament bulb (21) may, therefore, suffice.

A special light filter, which excludes confusing light of different wave-lengths from the source of illumination but passes the violet or ultraviolet rays, is interposed between the light source and the slide containing the material to be examined. Another filter, which passes yellow light but excludes shorter wave-lengths, is placed in or above the ocular of the microscope, between the slide and the eye of the observer. This shields the eye from the injurious effect of the ultraviolet rays and excludes the visible violet or blue light, which would otherwise prevent perception of the yellow light emitted by the fluorescing objects.

An ordinary bacteriological microscope may be used. The slides are examined in a dark or shaded room. Fluorescing bacilli may be seen with low power, but they must be distinguished morphologically from other objects naturally fluorescent or still retaining some stain, by the use of stronger magnification. The typical thin, bright, slightly curved rods may be readily recognized at about 200× magnification, such as is given by a 5× ocular with a high, dry objective. Special 20×, 40× or 60×, high, dry objectives have been recommended, but are not necessary. Oil immersion lenses are usually dispensed with, but a drop of nonfluorescent sandalwood oil between the microscope slide and the top of the substage condenser improves the illumination.

Sputum or other material, preferably after concentration, is thinly smeared on a glass slide. The slides may then be stained with any acid-fast staining technique, except that the carbol fuchsin is replaced by auramine. The staining solution is made by placing 1 g. of pure auramine powder in a flask, gradually adding 1,000 cc. of distilled water, shaking strongly until it is completely dissolved, and then adding 50 cc. of pure, liquefied phenol, and again shaking. A temporary clouding later settles out, leaving a clear yellow solution which keeps for a long time in the dark. Hagemann (9) recommends staining with auramine for fifteen minutes at room-temperature, and decolorizing with acid alcohol without counterstaining.

The following procedure, after Herrmann (10), has been used at the Olive View Sanatorium:

1: Fix with heat;
2: Flood with auramine solution, and steam for five minutes;
3: Wash in running water;
4: Decolorize in 70 per cent alcohol, containing 3 per cent hydrochloric acid until the preparation is colorless;
5: Wash in running water;
6: Dip in a 0.1 per cent aqueous solution of potassium permanganate (this solution remains usable for about a week after turning brown);
7: Wash in running water;
8: Dip in Löffler's alkaline methylene-blue solution;
9: Wash in running water;
10: Dry and examine with the fluorescence microscope.

TABLE 1

1,000 routine sputum smears

METHOD	POSITIVE	NEGATIVE	PER CENT POSITIVE
Ziehl-Neelsen	370	630	37.0
Fluorescence	445	555	44.5

TABLE 2

250 specimens negative by Ziehl-Neelsen

METHOD	POSITIVE	NEGATIVE	PER CENT POSITIVE
Fluorescence	29	221	11.6
Culture	60	190	24.0

Comparative examination of 1,000 duplicate smears of routine sputum specimens stained by the fluorescence and the usual carbol fuchsin method, at the Olive View Sanatorium, has generally confirmed the published reports (table 1). The fluorescence method gave over 20 per cent more positive findings than did the standard technique. Some slides, however, which showed a few organisms by the latter, failed to reveal them by the newer method. These discrepancies were probably due to technical error or to chance distribution of small numbers of organisms and insufficient examination, rather than to the existence of organisms which can be stained by one method and not by the other.

With the lower magnification used, it is theoretically possible to examine every part of the smear with the fluorescence microscope in less

than twenty minutes, instead of the eight hours or more required with the usual oil immersion magnification, and so not a germ should escape detection. Actually, however, this goal has not yet been reached by any worker. In 250 specimens negative to Ziehl-Neelsen, which were inoculated on Jensen's and Petragnani's culture media, there were more than twice as many positive cultures as were found on fluorescence microscopy (table 2). The majority of the fluorescent negative specimens which were positive on culture gave only a sparse growth on one out of several tubes planted. A single instance of apparently false positive fluorescence findings with negative culture may represent, instead, a false negative culture, such as may result from nonviable organisms or technical errors.

Fluorescence microscopy offers an interesting and valuable addition to bacteriological methods. It appears to be much more sensitive than the ordinary acid-fast staining methods, and consumes much less time in microscopic search. It may not yet completely supplant standard procedures for the detection of tubercle bacilli but constitutes a useful supplement for diagnostic and public health practice.

SUMMARY

Fluorescence microscopy is a new method for detecting tubercle bacilli. Its theoretical basis suggests advantages over the present microscopical procedures, both in speed and delicacy. An intense violet or ultraviolet source of radiation is required. The bacilli are stained with the fluorescent dye, auramine, and examined with an ordinary microscope equipped with special light filters. Practical experience confirms its predicted value. In 1,000 duplicate smears stained in parallel by the Ziehl-Neelsen and fluorescence methods, there were over 20 per cent more positive tests by the newer technique. In 250 parallel cultural and fluorescence microscopical examinations, the specificity of the latter was confirmed, although the cultural methods still gave considerably more positive findings.

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PULMONARY INSUFFICIENCY[1,2,3]

III. Cases Demonstrating Advanced Cardiopulmonary Insufficiency following Artificial Pneumothorax and Thoracoplasty

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In the study, reported in the preceding paper (1), of 31 cases that underwent thoracoplasty, it was found that most of the ventilatory insufficiency was already present prior to operation, and in a large proportion of cases increased only to a limited extent after recovery from operation. Respiratory gas exchange disturbance, when present before thoracoplasty, was often corrected following it. Cardiocirculatory disturbances, except in cases of therapeutic phrenic paralysis and fibrothorax, were in this series insignificant.

In no instance, if one excludes complications occurring during the immediate postoperative period, was it found in this series that an extreme degree of ventilatory insufficiency led to a severe degree of respiratory insufficiency, and eventually to manifestations of cardiocirculatory insufficiency. This sequence of events is, none the less, a distinct possibility, as pointed out by Gaubatz (2).

In the course of artificial pneumothorax, it is assumed that respiratory gas exchange remains normal and that the degree of ventilatory insufficiency is, as a rule, relative to the extent of the pulmonary collapse. Although theoretically possible, the development of cardiocirculatory failure is hardly mentioned in the literature. Recently a case of cardiac failure, occurring during the course of a bilateral artificial pneumothorax, has been reported (3). This complication, however, is extremely rare. In the present paper a contribution is made to the description and recognition of unusual combinations of ventilatory, respiratory and cardiocirculatory insufficiency caused by artificial pneumothorax and thoracoplasty, on the basis of two cases that we have had opportunity to study.

[1] From the Tuberculosis Service, First Division, Bellevue Hospital, and the Department of Medicine, College of Physicians and Surgeons, Columbia University, New York City.

[2] Under a grant from the Commonwealth Fund.

[3] Presented at the joint session of the National Tuberculosis Association, American Trudeau Society and the American Association for Thoracic Surgery, Cleveland, Ohio, June 6, 1940.

METHOD

The method used in the study of these cases is, on the whole, that described in the first and second papers of this series, with the following additions:

1: Residual air measurements were made according to a new method described recently (4).
2: In order to obtain a more complete description of the factors involved in oxygen transport from the alveoli to the arterial blood, the oxygen dissociation curve was experimentally determined according to a technique described many years ago by one of us (5), with a few minor changes suggested recently by Dill *et al.* (6).
3: In one case, the effect of exercise upon venous pressure, vital capacity, blood pressure and pulse rate was estimated separately.
4: In the same case, the cardiac index (cardiac output per square meter of body surface) was measured by a technique described previously (7).

I. Extreme degree of anoxia, early cardiac failure, caused by artificial pneumothorax in a patient with chronic pulmonary tuberculosis complicated by unrecognized pulmonary emphysema.

CASE REPORT

Case 1: S. P. (ht. 180 cm.; wt. 63.3 kg.; body surface area 1.81 sq. m.), a young male twenty-seven years of age, had had a known chronic pulmonary tuberculosis with frequent haemoptyses since 1929. Rest cure, right artificial pneumothorax and a temporary crushing of the phrenic nerve proved to be ineffective in closing a cavity at the right apex, apparent source of the repeated bleeding. Finally a five-upper-rib thoracoplasty successfully collapsed the cavity. In August, 1939, however, the patient was readmitted for recurring haemoptyses. Roentgenograms of the chest at this time revealed a small cavity at the left apex, and as the patient, on limited activity prior to admission, had never seriously complained of dyspnoea, an artificial pneumothorax was started on the left side.

A small degree of collapse was maintained without any untoward reaction at first. After four weeks, however, the amount of collapse still being small and intrapleural pressure negative (figure 1), very severe frontal headaches appeared, which were at first attributed to sinusitis. After another week, he became nervous, restless, started to vomit, and a mild degree of cyanosis of lips and nailbeds was first noticed. There was no complaint of dyspnoea.

Cyanosis increased suddenly on November 10, 1939. Mild delusions with personality changes and prostration appeared (8), together with a slight fever; these suggesting that the whole picture might be caused by a tuberculous

FIG. 1 FIG. 2

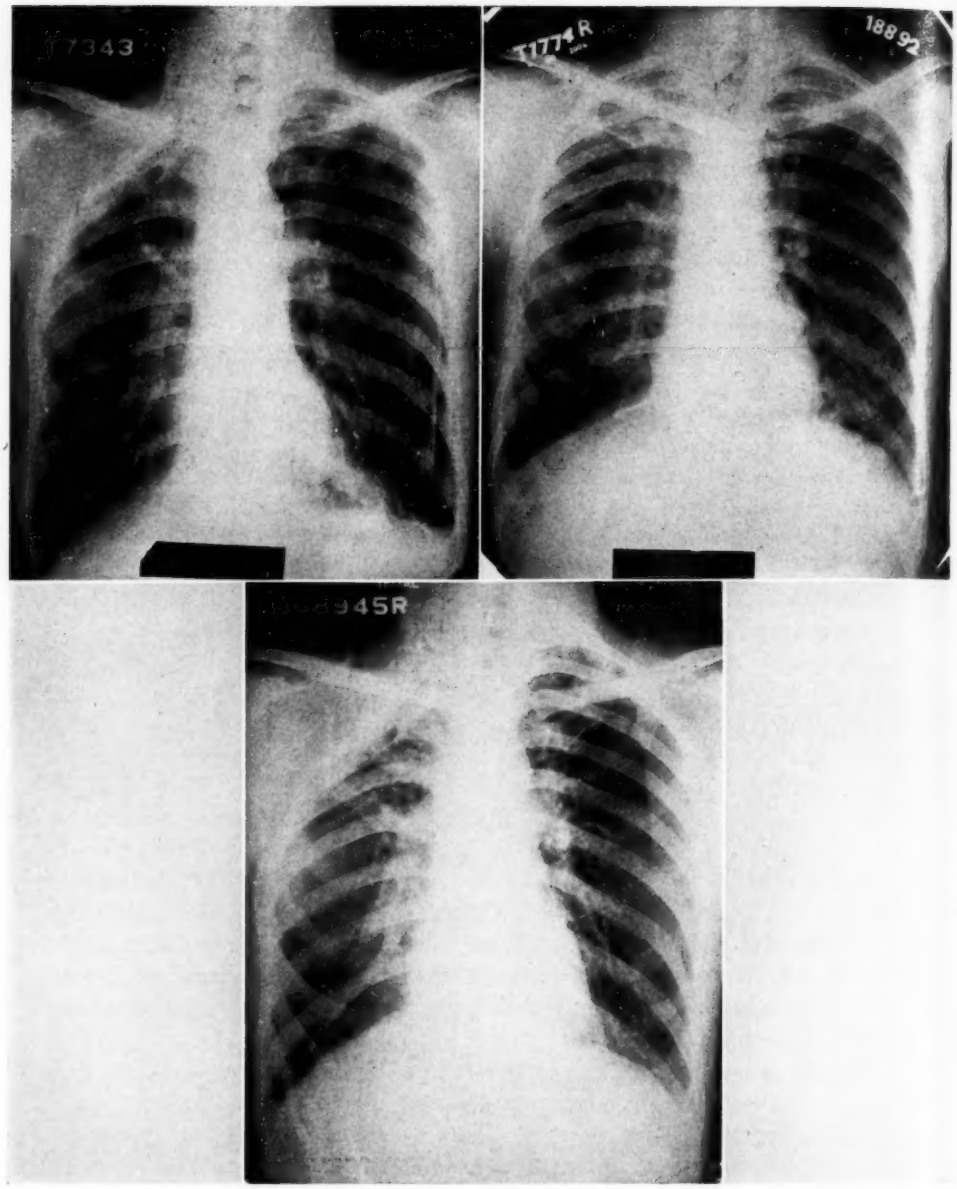


FIG. 3

FIG. 1. S. P. Roentgenogram taken shortly before development of acute anoxia.

FIG. 2. S. P. Roentgenogram taken in 1934. Note scattered nodular shadows throughout lower left and middle right lung fields.

FIG. 3. S. P. Roentgenogram taken in 1939. Scattered nodular shadows are no longer visible.

meningitis, although the probability of acute anoxia was also considered. The latter was confirmed by study of the arterial blood, which revealed an extreme degree of anoxaemic anoxia, the oxyhaemoglobin being at the very low level of 57.8 per cent of complete saturation (table 1). By that time, the pulse, which had been regular at a rate of about 110 per minute, became very rapid and irregular, and an impure auricular flutter was revealed by electrocardiogram.

TABLE 1

S. P.—Findings during period of acute anoxia

DATE	ARTERIAL BLOOD O_2 HAEMOGLOBIN SAT. %	PULSE RATE/MIN.	RESP. RATE/MIN.	VENOUS PRESSURE	ELECTROCARDIOGRAM	SYMPTOMS AND SIGNS	TREATMENT
				mm. H_2O			
11/10/39	57.8	110–140	22–24	140	Impure auricular flutter.	Anorexia, vomiting, restlessness, headache, delusions, personality changes, cyanosis.	Artificial pneumothorax reexpanded —550 cc. removed. O_2 tent O_2 conc. 65%
11/11/39	80.3 (out of tent)	100	22–26		Prominent T in leads 1, 2, 3; inverted T in lead 4 (apex).	Restlessness, feels better.	O_2 tent O_2 conc. 65%
11/14/39	81.5 (out of tent) 100 (in tent)	96	20	85		Slight headache, comfortable.	O_2 tent O_2 conc. 50%
11/17/39	88.6 (out of tent)	92	20			Mentally clear, comfortable, no cyanosis outside tent.	O_2 tent O_2 conc. 50%
11/19/39				45	Prominent T in all leads.	Comfortable.	O_2 by nasal catheter

The only other evidences of cardiac disturbance were a negative fluid balance and the high level of venous pressure at 140 mm. water. Breathing was rapid, shallow, slightly irregular, apparently not labored.

Immediate reëxpansion of the lung was decided upon, and was almost completed after withdrawal of 550 cc. of air. The patient was put in an oxygen tent, where the concentration of oxygen was maintained around 65 per cent. No other treatment was instituted.

The result was striking (table 1). Within twelve hours, the pulse rate dropped to 90 and normal sinus rhythm was restored. The arterial oxyhaemoglobin saturation (after the patient had been removed from the tent for a half hour) was 80.7 per cent. In the next four days the patient improved rapidly. He became mentally clear, vomiting ceased and headache was less pronounced. Venous pressure returned to normal. Fluid balance was restored. On the eighth day, when he was removed from the tent, the arterial oxyhaemoglobin saturation was 90 per cent, and he returned rapidly to a stable condition.

In short, following the institution of a small artificial pneumothorax, a state of anoxia developed, first insidiously, then acutely. Acute anoxia led to

TABLE 2

Lung volumes

Subject	S. P.					E. T.		
State	Flat			Standing		Flat		Standing
	Predicted	Observed (1)	Observed (2)	Observed	Observed*	Predicted	Observed	Observed
Complementary air, liters		1.57		1.36	1.55		.88	.81
Reserve air, liters		.52		.84	.95		.31	.31
Residual air, liters	1.25	3.66	3.29			1.01	1.00	
Vital capacity, liters								
Observed	5.05	2.02	2.15	2.02	2.69	4.07	1.03	1.10
Calculated		2.09		2.20	2.50		1.19	1.12
Total capacity, liters	6.30	5.75	5.44			5.08	2.19	
Ratio $\frac{\text{Residual Air}}{\text{Total capacity}} \times 100$	19.9	63.6	60.4			19.9	45.7	

* After bronchodilator.

cardiac manifestations which, along with the other symptoms of oxygen want, were rapidly controlled by reëxpansion of the lung and oxygen therapy.

Why such a small artificial pneumothorax should have resulted in such dramatic manifestations of anoxia became clear when, one month later, a study of the patient's pulmonary and circulatory capacity was completed (tables 2 to 7 and chart 1).

This revealed a state of advanced emphysema, residual air being 64 per cent of a total lung volume still very large. The maximum breathing capacity being only 32 liters per minute and the breathing reserve at rest being 74.3 per cent of the maximum breathing capacity, it was not surprising to find that a moderate degree of exercise precipitated an intense dyspnoea, lasting for a

TABLE 3

Maximum breathing capacity

SUBJECT	NORMAL RANGE IN MALE SUBJECTS		S.P.			E.T.	
State	Standing		Flat	Standing		Flat	Standing
	Mean	Standard deviation	Observed	Observed	Observed*	Observed	Observed
Maximum breathing capacity, liters/minute	154.0	30.9	32.3	31.8	45.7	31.1	32.8

* After bronchodilator.

TABLE 4

Ratio $\frac{\text{Breathing reserve}}{\text{Maximum breathing capacity}} \times 100$. *Intensity and duration of dyspnoea at rest and during recovery from exercise*

SUBJECT	S. P.						E. T.					
State	Basal	Rec. 1	Rec. 2	Rec. 3	Rec. 4	Rec. 5	Basal	Rec. 1	Rec. 2	Rec. 3	Rec. 4	Rec. 5
Ratio $\frac{\text{B.R.}}{\text{M.B.C.}} \times 100$	74.3	—	47.0	50.0	56.0	56.0	84.2	55.8	63.0	70.0	70.0	74.0
Dyspnoea	0	+++	+++	++	+	+	0	++	+	0	0	0

TABLE 5

Gas exchange at rest and during standard exercise

SUBJECT	CONTROL GROUP*				S. P.		E. T.		
Date					12/18/39		11/19/39		11/21/39
State	Basal		Exercise		Basal	Exercise	Basal	Exercise	Basal
	Mean	Variation	Mean	Variation					
Ventilation, lit./min./sq.m.B.S.**	3.20	(2.40– 4.54)	9.70	(7.27– 13.37)	4.56	8.87	3.69	8.48	3.59
CO_2 output, cc./min./sq.m.B.S.***	101.9	(86 –148)	318.0	(220 –427)	114.0	262.0	121.0	221.0	128.0
cc./lit. ventilation	37.0	(29.8 – 45.1)	36.7	(32.6 – 42.0)	29.0	34.4	38.1	30.4	37.9
O_2 intake, cc./min./sq.m.B.S.	128.6	(108 –159)	459.6	(354 –590)	144.0	371.0	161.0	319.0	152.0
cc./lit. ventilation	46.8	(40.1 – 57.1)	54.8	(44.9 – 62.6)	36.7	48.7	50.6	43.8	49.0
R.Q.	.78	(.72– .87)	.66	(.61– .75)	.79	.71	.76	.69	.77

* The control group consisted of a group of 15 hospital patients with apparently normal pulmonary and circulatory function.

** Saturated gas at 37°C. and prevailing barometric pressure.

*** Dry gas at 0°C. and 760 mm. Hg.

TABLE 6

Arterial blood studies

Subject	Control group*				S. P.				E. T.						
Date					12/18/39		4/9/40	4/19/40	11/16/39		11/19/39		2/17/40	4/23/40	
State	Basal		Recovery		Basal	Rec.	Basal	Basal	Basal	Rec. 1	Basal	Rec. 1	Non-basal, 2 hours after meal	Basal	Rec.***
	Mean	Variation	Mean	Variation											
CO_2 Content, vol. %	52.0	(48.5 – 56.3)	47.8	(44.8 –51.5)	56.4	51.4	55.9	54.4	56.4	55.3	57.5	58.5	60.7	57.2	58.8
CO_2 Content at 40 mm. Hg, vol. %	50.6	(48.0 – 55.1)	46.6	(43.7 –50.1)	53.0	47.6	51.4	51.4	—	—	53.0	48.6	53.0	51.4	50.8
pHs	7.43	(7.40– 7.47)	7.40	(7.36– 7.43)	7.40	7.36	7.39	7.41	—	—	7.40	7.33	7.38	7.37	7.35
pCO_2 art., mm.	43.7	(39.1 – 47.2)	43.0	(39.7 –45.5)	46.0	48.0	49.3	45.9	—	—	46.4	57.0	54.7	51.7	56.0
pCO_2 alv., mm.	—	—	—	—	—	—	47.6	43.4	—	—	—	—	56.8	—	—
pCO_2 art.-alv.**	+0.7	(−4.7 – +5.7)	—	—	—	—	+1.7	+2.5	—	—	—	—	−1.5	—	—
O_2 Haemoglobin Capacity, vol. %	17.1	(13.2 – 20.7)	17.9	(14.2 –20.7)	19.9	20.9	18.8	20.0	21.1	21.2	20.2	20.5	19.8	20.6	20.6
$\frac{O_2 \text{ Haemoglobin Content}}{O_2 \text{ Haemoglobin Capacity}} \times 100.$	96.2	(95.3 – 98.7)	95.8	(93.2 –98.0)	89.0	95.7	92.5	94.0	92.4	69.1	91.3	68.3	90.4	89.4	79.4
pO_2 art., mm.**	83.3	(78.2 – 94.6)	—	—	—	—	—	60.2	—	—	—	—	61.1	—	—
pO_2 alv., mm.**	101.5	(94.3 – 110.7)	—	—	—	—	—	87.0	—	—	—	—	79.7	—	—
pO_2 art.-alv.**	−18.2	(−0.3 – −32.5)	—	—	—	—	—	−26.8	—	—	—	—	−18.6	—	—
pO_2 at half saturation, at art. pHs and rectal temperature	26.0	(25.0 – 26.9)	—	—	—	—	—	25.1	—	—	—	—	26.6	—	—

* The control group consisted of a group of 15 hospital patients without pulmonary or cardiac disease.

** Figures from Dill *et al.* (5).

*** Recovery from 15 steps exercise.

period of four to five minutes after its cessation. Thus the degree of *ventilatory* insufficiency was marked.

In contrast, there was at this time but little evidence of *respiratory* insufficiency at rest, and none during and after exercise: the rate of oxygen removal and carbon dioxide output per liter of air ventilated was somewhat low at rest, as found in the majority of cases with pulmonary emphysema, and the arterial blood was slightly unsaturated; but during exercise the ventilation appeared very effective and the aeration of the blood normal, as shown by the large increase in the rate of oxygen removal from inspired air and the normal

TABLE 7

State of circulation

SUBJECT	S. P.		E. T.							
	Infusion test		Infusion test		Exercise test					
	Before	At End	Before	At End	Before	Rec. 1	Rec. 2	Rec. 4	Rec. 5	Rec. 9
Venous pressure, mm. H_2O.....	36	40	45	115	90	170	135	120	110	105
Pulse rate.....	92	102	100	100	188	122	120	108	—	90
Blood pressure, mm. Hg.....	125/80	—	—	—	132/70	170/100	170/110	150/104	154/92	135/90
Circulation time, sec....	15	15	20	—	—	—	—	—	—	—
Vital capacity, liters.....	2.02	1.92	.91	.74	—	—	—	—	—	—
Vital capacity, decrease %..	—	4.7	—	18.8	—	—	7.6	—	—	3.3
Cardiac index.....	—	—	1.87	—	—	—	—	—	—	—

saturation of the blood. It was remarkable that at this time all tests of cardiocirculatory capacity indicated a normal state: the venous pressure was low and remained low following the infusion test and the vital capacity did not change more than 4 per cent. Confirmation of the diagnosis of emphysema was provided by the characteristic changes of obstructive breathing as revealed by spirographic tracings (9) and the small amplitude of motion of both diaphragms, jerky in character during deep breathing, as revealed by fluoroscopy.

COMMENT

With these findings, the following reconstruction of the sequence of events seemed warranted:

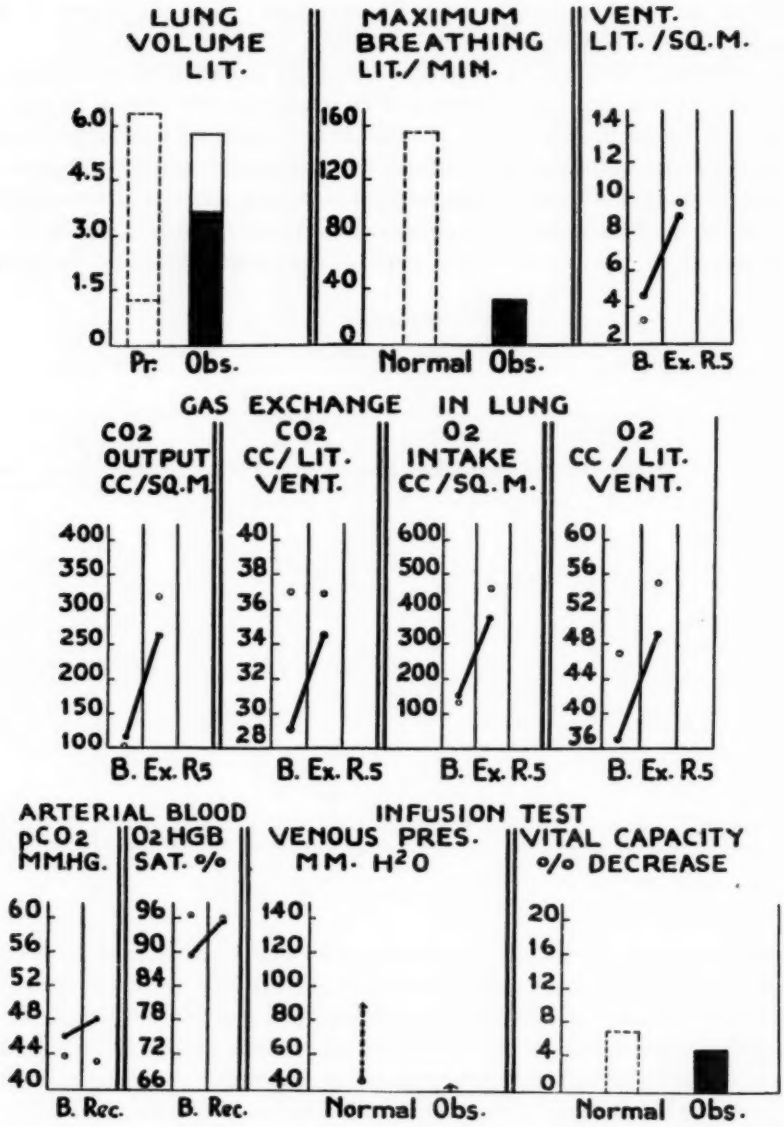


CHART 1. S. P. Pulmonary and circulatory capacity, December, 1939. Broken lines and open circles indicate predicted or average normal values in control group.

1: Repeated haemoptyses resulted in scattered fibrosis, which later was obscured on the roentgenograms by associated pulmonary emphysema (figures 2 and 3).

2: Following the institution of a small artificial pneumothorax, a proportion of the normally and actively functioning lung parenchyma collapsed, and as a result respiratory insufficiency, with acute anoxia and in its wake cardiac failure, developed.

This case is instructive in many respects, and we should like to call attention to the following practical considerations:

(*a*) The advanced state of pulmonary emphysema which may result in early life from protracted chronic pulmonary tuberculosis with repeated haemoptyses and the value of simple measurements for its recognition.
(*b*) The narrow margin of safety in emphysematous subjects, with the precipitation of acute respiratory insufficiency, when a small part of the remaining normal lung tissue is encroached upon.
(*c*) The possible prediction of the intensity of dyspnoea by simply measuring the breathing reserve at rest, and
(*d*) Finally, the deceptive character of manifestations of anoxaemic anoxia (10, 11), the part played by it in the development of cardiac failure (11, 12, 13, 14), and the striking effect of oxygen therapy in controlling this complication (15).

II. Severe degree of respiratory insufficiency due to restriction of chest motion, precipitated by mild exertion in a patient with kyphoscoliosis resulting from a thoracoplasty performed in early adolescence.

CASE REPORT

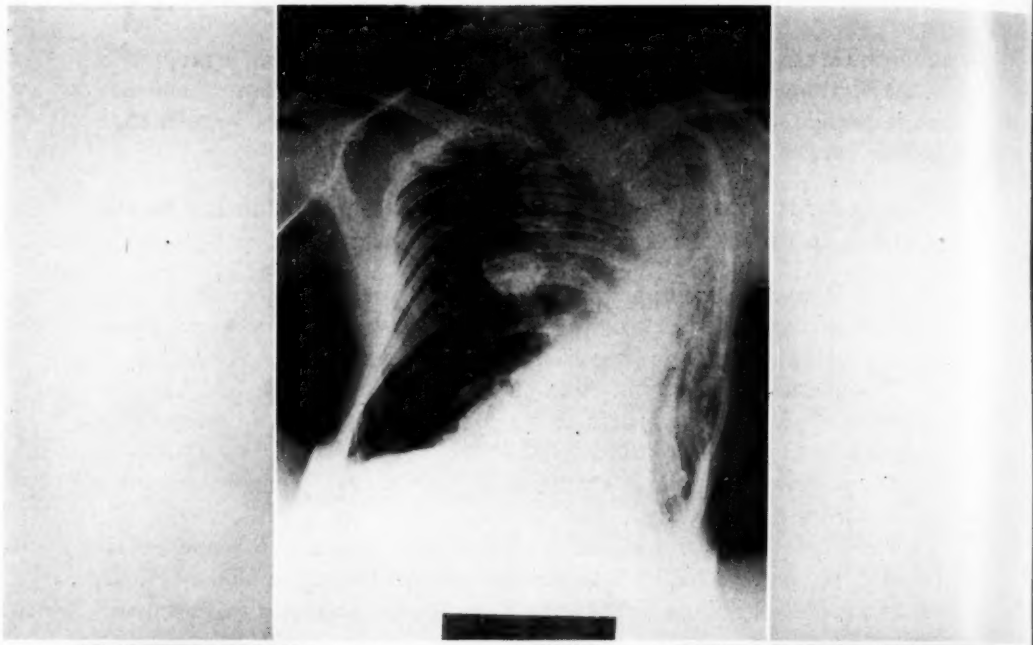
Case 2: The second case is that of E. T. (ht. 163 cm.; wt. 48.0 kg.; body surface area 1.50 sq.m.), a young male of twenty-one, who developed an extreme degree of scoliosis following a thoracoplasty performed at the age of twelve (16). More or less on reduced activity since that age because of intermittently recurring positive sputum, he noticed for the first time during the preceding summer, while working as a bell boy, dyspnoea and cyanosis on moderate exertion. This prompted his admission to our service.

Physical examination and roentgenogram (figure 4), in addition to providing information regarding the anatomical characteristics of his deformity, revealed a type of breathing strictly diaphragmatico-abdominal: there was no motion of the ribs nor change in their direction or in the width of the rib interspaces on the right side in deep respiration. The right diaphragm had a large excursion and apparently was the sole source of air displacement in the lungs.

A striking feature of his physical behavior was the marked dyspnoea and cyanosis developing upon mild exertion.

The studies carried out on this patient sought to explain these attacks; as well as to evaluate the factors of (*a*) ventilatory restriction, (*b*) emphysema,

FIG. 4



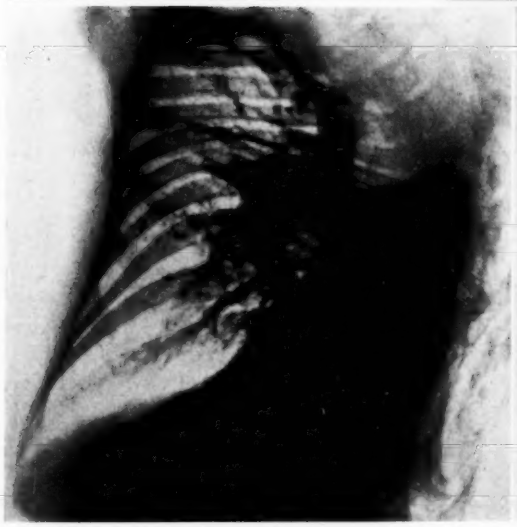


FIG. 5 FIG. 6

FIG. 4. E. T. Roentgenogram taken in November, 1939, nine years after extensive left thoracoplasty.

FIG. 5. E. T. Visualization by diodrast method of heart and large vessels (Robb and Steinberg). A. P. roentgenogram showing rotation of the heart toward the left simulating the appearance seen in right anterior oblique position. Note normal size of right auricle and ventricle and enlargement of pulmonary artery, right pulmonary artery and subdivisions.

FIG. 6. Visualization by diodrast method. Oblique view. Note enlarged pulmonary conus and pulmonary artery, the dwarfed left pulmonary artery, and the enlarged right pulmonary artery seen on end.

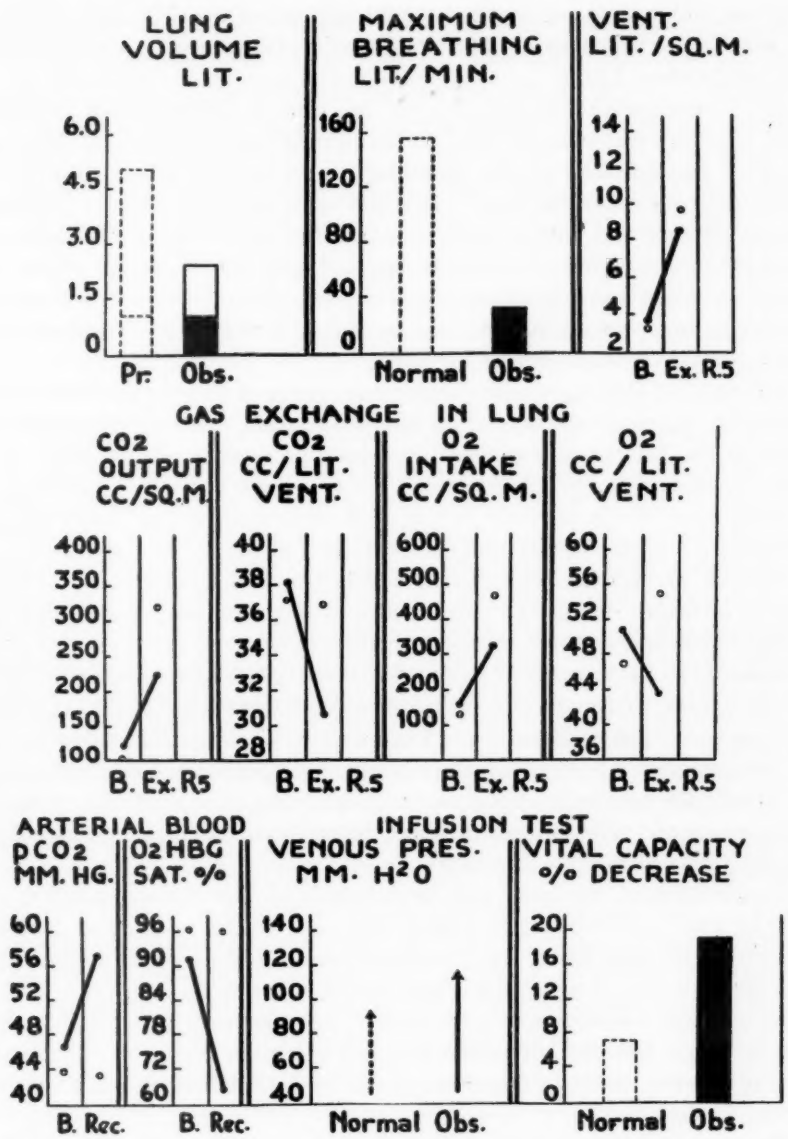


CHART 2. E. T. Pulmonary and circulatory capacity, November, 1939. Broken lines and open circles indicate predicted or average normal values in control group.

(*c*) cardiac insufficiency, usually thought to exist in these cases (tables 2 to 7, chart 2).

The degree of emphysema, as shown by the proportion of residual air in the

total lung volume (45 per cent), was mild, and not of the obstructive type, as was revealed by spirograms. The vital capacity, as expected, was considerably reduced, to about 1 liter.

At rest the breathing reserve was 85 per cent of the maximum breathing capacity which was exactly equal to that in the previous case, 32 liters per minute. The definitely greater breathing reserve in this patient is due to the low level of ventilation required. Two factors contribute to this: (*1*) a greatly reduced stature and weight, and (*2*) a remarkable efficiency of ventilation indicated by the high rate of oxygen removal and carbon dioxide output per liter of air ventilated. Respiratory insufficiency at rest was present, however: the oxyhaemoglobin saturation being somewhat below normal range and the carbon dioxide tension slightly elevated.

During and following exercise, an extreme degree of respiratory insufficiency developed, characterized by: (*a*) an intense cyanosis; (*b*) the considerable decrease in the arterial oxyhaemoglobin saturation down to 69 per cent; (*c*) a large increase in carbon dioxide tension; (*d*) a large *decrease* in efficiency of ventilation, shown in the drop in rate of oxygen removed and carbon dioxide excreted; (*e*) failure of the usual increase in ventilation during exercise.

As soon as exercise stopped, the ventilation increased greatly, and the dyspnoea, severe during the first minute of recovery, was less pronounced during the second and was absent from the third on.

Tests of circulatory capacity showed a circulation time at the upper level of normal figures, a normal venous pressure which increased but slightly after the infusion test. But a decrease of 19 per cent of vital capacity following this test was suggestive evidence of latent pulmonary congestion. The response of the circulation to exercise failed to reveal any persistent evidence of cardiac embarrassment. The venous pressure, high during the first minute of recovery, returned rapidly to normal.

Visualization of the heart and large vessels by the diodrast method was done by Doctors Robb and Steinberg, and showed (*1*) a rotation of the heart toward the left simulating the appearance seen in right anterior oblique position (figure 5); (*2*) a right auricle and ventricle normal in size; (*3*) a marked enlargement of the pulmonary conus and of the pulmonary artery and its right branch, and a dwarfed left pulmonary artery (figures 5 and 6); (*4*) the pulmonary veins on the right questionably enlarged; (*5*) left auricle and ventricle normal in size.

The electrocardiogram, except for right axis deviation, was normal.

COMMENT

In this patient with extreme chest deformity, the degree of emphysema was moderate; hypertension in the lesser circuit and latent pulmonary congestion (17) were probably incidental to adjustment of the heart and

large vessels to the intrathoracic condition and to the extensive collapse of lung on the left side. They were not associated with any significant evidence of cardiac embarrassment upon increased load and exertion.

The cause of the acute syndrome of respiratory insufficiency was to be looked for elsewhere.

Defective mechanics of breathing has been recognized in recent years as an important cause of dyspnoea in structural disturbances of the thorax. Chapman, Dill and Graybiel (18) have recently published an excellent study of deformities of the chest in which this same conclusion is reached. The marked restriction of ventilation in our case, persisting during body motion, in spite of increased stimulus to the respiratory centre by high carbon dioxide tension, and the release of the restriction after cessation of the exercise also point definitely to the importance of such mechanism.

It is probable that during exercise the diaphragmatic excursion was limited by contraction of the abdominal muscles and, the chest wall being structurally fixed, no possible compensation could take place. In brief, restriction of chest motion may be the cause of extreme respiratory insufficiency, by limiting ventilation and thus aeration of the blood. It may further precipitate this failure by interfering with the return of blood to the right heart and its circulation in the lungs, but we have no proof on which to base this assertion (19, 20, 21).

The span of life in this group of patients has been known since Hippocrates' time to be short. After a series of attacks of dyspnoea with cyanosis and fainting spells, they are doomed to early and sudden death. Deterioration of the respiratory and vasomotor centres is suggested by reports of sudden exitus following injection of morphine and vasomotor crises following breathing of an atmosphere low in oxygen (18). Cardiac failure of the type associated with *cor pulmonale* and Ayerza's syndrome is exceptional (18).

It was possible in this case to conclude with an anatomical study, as the patient died about a year later. A few weeks before, he developed progressively an extreme degree of arterial anoxaemia, not relieved by oxygen therapy. No symptoms of heart failure were observed.

The additional factor that caused the patient's death was unusual, and consisted in a thrombosis of the right pulmonary artery. This apparently began in the vessels of the wall of an encapsulated caseous focus and extended proximally. This focus had been noted on the X-ray film as a round dense shadow in the right lung field along the path of the pulmonary vessels, but its nature was unexplained during life.

The pathological findings, aside from the thrombosis, included a moderate degree of emphysema in the right lung, a considerably hypertrophied right heart with dilatation of both auricular and ventricular cavity; no evidence of chronic passive congestion in the liver, spleen, etc.

SUMMARY

1. Two cases are presented, which illustrate different aspects of ventilatory, respiratory and circulatory insufficiency associated with collapse therapy.

2. The first case demonstrates the following: (*a*) the extreme degree of emphysema that may develop in young subjects with chronic pulmonary tuberculosis; (*b*) the small margin of safety that exists in these cases when treated with pneumothorax; (*c*) the development of profound arterial anoxaemia without accompanying increase in dyspnoea; (*d*) the insidious and variable symptomatology associated with anoxaemia; (*e*) the effect of anoxaemia in precipitating cardiac failure.

3. In the second case the points of chief interest are: (*a*) marked kyphoscoliosis developing in a young subject following extensive thoracoplasty; (*b*) physical dysfunction caused by disturbance in mechanics of breathing; (*c*) minimal evidence of ventilatory and respiratory insufficiency when the patient was examined under resting conditions; (*d*) extreme degree of both ventilatory and respiratory insufficiency during even light exertion, due primarily to failure of the ventilatory mechanism of the chest; (*e*) insignificant evidence of cardiocirculatory failure.

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OXYGEN PERCENTAGE IN PNEUMOTHORAX AND PNEUMOPERITONEUM GASES[1,2]

Evidence of Low Oxygen Tension in Tuberculous Tissues

HERBERT PUGSLEY

With the technical assistance of Ross Benham

The primary purpose of this report is to present evidence which indicates that the oxygen tension is very low in tuberculous tissues in the pleura and peritoneum. Since the rate of growth of tubercle bacilli is retarded in the presence of a low oxygen tension, this may be an important factor in the resistance of the host to the tuberculous infection.

This is an experimental study in rabbits of the percentage of oxygen and carbon dioxide found in artificial pneumothorax and pneumoperitoneum under the following conditions: (*a*) uncomplicated, (*b*) complicated by tuberculous pleuritis or peritonitis, and (*c*) complicated by sterile pleuritis. It is also a clinical study of the same gases in the closed pneumothorax of patients with pulmonary tuberculosis.

The oxygen in a closed pneumothorax tends to be in pressure equilibrium with the oxygen in solution in the tissues of the pleura. Therefore, the percentage of oxygen in a closed pneumothorax is an indication of the percentage of oxygen in the pleural tissues.

According to Wright's Applied Physiology (1) gaseous interchange occurs between the oxygen in the pleural sac and the oxygen in the venous blood so as to tend to establish pressure equilibrium on the two sides of the pleural membrane. He states that the proportion of oxygen in an uncomplicated closed pneumothorax is about 6 per cent.

Several investigators (2 to 11) have studied the gases in uncomplicated pneumothorax in animals and in the pneumothorax of patients with pulmonary tuberculosis. It was noted by some that, in patients, the oxygen percentage falls to low values in pneumothorax complicated by tuberculous pleuritis with effusion.

Others (12, 13) have studied the gases in uncomplicated pneumo-

[1] From the Muskoka Hospital, Gravenhurst, Ontario, Canada.

[2] Presented at a meeting of the Academy of Medicine, Toronto, Canada, January 21, 1941.

peritoneum in animals and concluded that the tension of oxygen in the pneumoperitoneum probably corresponds to that in the surrounding tissues.

No record could be found in the literature of an experimental study in animals of the oxygen percentage in pneumothorax or pneumoperitoneum following the introduction of a tuberculous pleuritis or peritonitis.

TECHNIQUE OF GAS ANALYSIS

In rabbits the gas sample was collected from the pneumothorax or pneumoperitoneal space by the use of a sterile 50 cc. Luer Lok type syringe with a stop-cock attachment and lock type connection. The walls of the syringe were lubricated with sterile vaseline to insure air tightness. The sample was withdrawn just before giving a refill. After inserting the needle connected to the stop-cock, a few cubic centimetres of gas were aspirated, then the stop-cock was closed and this gas was discarded to avoid collecting in the sample the small fraction of air present in the needle and connection. A sample of about 25 cc. was then withdrawn for analysis.

In patients a similar technique was followed except that a 100 cc. syringe was used and about 60 cc. of gas were withdrawn for analysis. The large size of the sample contributes to the accuracy of the determinations.

The gas sample was transferred to a Hempel burette where volume determinations were made. The burette was connected to a Hempel pipette containing 40 per cent sodium hydroxide for the removal of carbon dioxide, the loss of volume was measured and then it was connected to a pipette containing alkaline pyrogallol for the removal of oxygen and the percentage of each gas in the sample was thus determined.

OBSERVATIONS ON RABBITS

Technique

Rabbits weighing 5 to 7 pounds were usually used. As the two pleural sacs are not connected, a unilateral pneumothorax can be induced.

A small pneumothorax apparatus, employing the principle of water displacement of gas by gravity, was used to give the refills. The cylinder was graduated to units of 10 cc. A valve led to a water manometer for pressure readings.

Pneumothorax was induced and maintained on the right side with nitrogen refills, aseptic technique being used. About 60 cc. of gas were given in the initial filling. The animals were fluoroscoped every one to two days to determine the position of the mediastinum and the presence or absence of a pleural effusion. Following this examination a refill was given, the size of which was estimated by the position of the mediastinum and the final intrapleural pressures; the latter were always kept on the negative side. The pneumothorax was maintained in all cases until the animal was killed.

A similar technique was followed for pneumoperitoneum, except that the size of the refill was determined by the fluoroscopic appearance of the gas pocket in the abdomen, the refills were much larger than those for pneumothorax and the pressure was on the positive side.

In the group of rabbits in which pneumothorax was complicated by tuberculous pleuritis the following technique was used. Uncomplicated pneumothorax was maintained for several days and the percentage of carbon dioxide and oxygen in the sac determined. Then a suspension of the human type of tubercle bacilli was injected into the pneumothorax space and the pneumothorax was continued, as described above, until the animal was killed. Tuberculous peritonitis complicating pneumoperitoneum was induced in a similar manner.

The human type of tubercle bacillus was selected for these experiments because it is only slightly virulent for the rabbit (14, 15), the disease produced is usually limited and it reaches its maximum in the third or fourth week after which it usually subsides.

We are indebted to the Saranac Laboratory for the transplant of their human type culture H63, which was used in this investigation. A weighed amount of the tubercle bacilli from a freshly grown culture was placed in sterile physiological saline solution to form a fairly uniform suspension to the concentration of 1 mg. of tubercle bacilli per 1 cc. of saline solution. The dose of tubercle bacilli injected into the pleural or peritoneal sac varied from 0.5 mg. to 7 mg.

At the selected time the rabbits were killed by chloroform anaesthesia and a postmortem examination performed including bacteriological and histological examinations of the pleural or peritoneal tissues.

Results

Uncomplicated artificial pneumothorax was maintained in 2 rabbits for three months and six months respectively during which period samples of pneumothorax gas were analyzed at least once weekly. The percentage of oxygen and carbon dioxide in the samples remained fixed within a narrow range; neither showed any tendency to change during the entire period. The oxygen values varied between 7.0 and 9.2 per cent and the carbon dioxide between 5.0 and 7.3 per cent. At postmortem examination the pleura was found to be normal in both cases.

Since the oxygen in a closed pneumothorax space is in pressure equilibrium with the oxygen in solution in the tissues of the pleura, one may conclude that the tension of oxygen in solution in the normal pleural tissues of the rabbit is about 8 per cent of an atmosphere.

Pneumothorax complicated by tuberculous pleuritis was studied in a total of 20 rabbits. The range of oxygen and carbon dioxide values in

the samples taken before the introduction of the tuberculous infection was approximately the same as that described above. The rabbits were killed at various times between the seventh and one hundred and eleventh day after the production of the tuberculous pleuritis; the pneumothorax was maintained and samples of gas were analyzed at frequent intervals during the entire period. A serous pleural effusion complicating the pneumothorax developed in 15 of the 20 rabbits; the effusion appeared between the sixth and sixteenth days following the introduction of the infection. In the remaining 5 rabbits an effusion did not appear. At

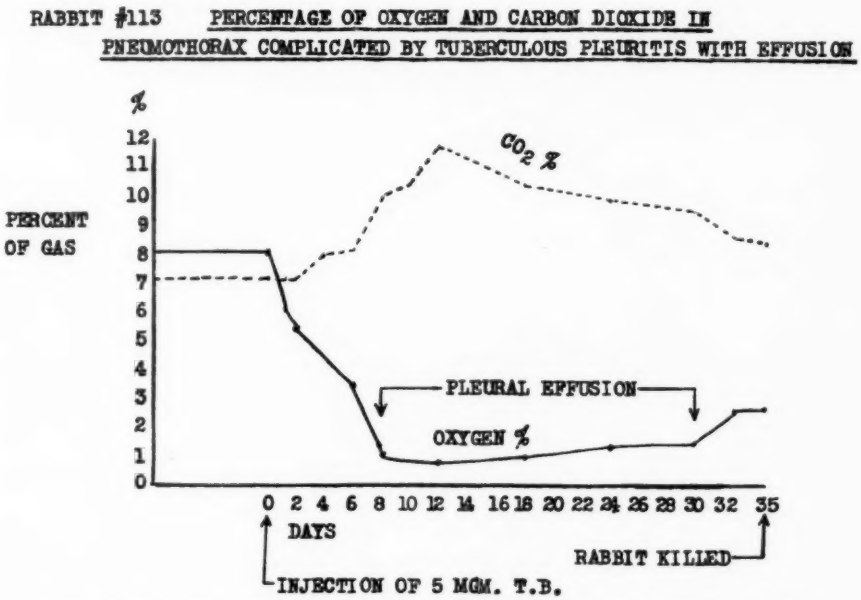
RABBIT #113 PERCENTAGE OF OXYGEN AND CARBON DIOXIDE IN PNEUMOTHORAX COMPLICATED BY TUBERCULOUS PLEURITIS WITH EFFUSION
%
PERCENT OF GAS
CO_2 %
PLEURAL EFFUSION
OXYGEN %
0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 35
DAYS
RABBIT KILLED
INJECTION OF 5 MGM. T.B.

CHART 1. Percentage of oxygen and carbon dioxide in pneumothorax complicated by tuberculous pleuritis with effusion

postmortem examination all 20 rabbits had tuberculous pleuritis of varying extent complicating the pneumothorax. In no case was there a secondary infection.

Chart 1 shows the percentage of oxygen and carbon dioxide in a pneumothorax complicated by tuberculous pleuritis with effusion. The oxygen percentage is represented by the solid line and the carbon dioxide by the broken line. A pleural effusion appeared on the eighth day after the introduction of the infection and was absorbed on the thirtieth day. The oxygen percentage fell to around 1 per cent during the period of the

effusion and rose to about 2.5 per cent following the absorption of the fluid. We believe that this reflects a similar fall in the oxygen tension in the surrounding tuberculous tissues of the pleura. The rabbit was killed on the thirty-fifth day and figure 1 is a photograph of the pleural sac of this rabbit. Some of the nodules, when incised, exuded caseous pus which was positive for acid-fast bacilli. Microscopical sections showed a granulomatous reaction; blood capillaries were sparse and there were occasional giant cells. These findings represent the typical response in the rabbits which developed a pleural effusion.

FIG. 1. Rabbit no. 113. Right pleural sac. Tuberculous pleuritis

In all cases in which a pleural effusion appeared, the oxygen values began to fall within a few days after the introduction of the infection, reached about 1 per cent or less when the effusion appeared, and remained there until the fluid was absorbed. Following the absorption of the pleural fluid and concurrent with the healing of the tuberculous tissues in the pleura the oxygen percentage slowly increased; it usually rose to about 5 per cent two or more weeks after the pleural fluid absorbed at which time histological sections of the pleura showed numerous fibroblasts and blood capillaries.

Chart 2 shows the percentage of oxygen and carbon dioxide in pneumothorax complicated by dry tuberculous pleuritis, that is, a pleural effusion did not appear. This proves that the oxygen percentage falls in the

absence of a pleural effusion. At necropsy several tuberculous nodules were found in the pleura. The remaining 4 rabbits in which an effusion did not appear showed a similar fall in oxygen values.

In addition to nitrogen refills, air and oxygen refills were tried in several rabbits with tuberculous pleuritis and the percentage of oxygen in the pleural space twenty-four hours after the refills was the same as that found after the use of nitrogen, showing that pressure equilibrium with

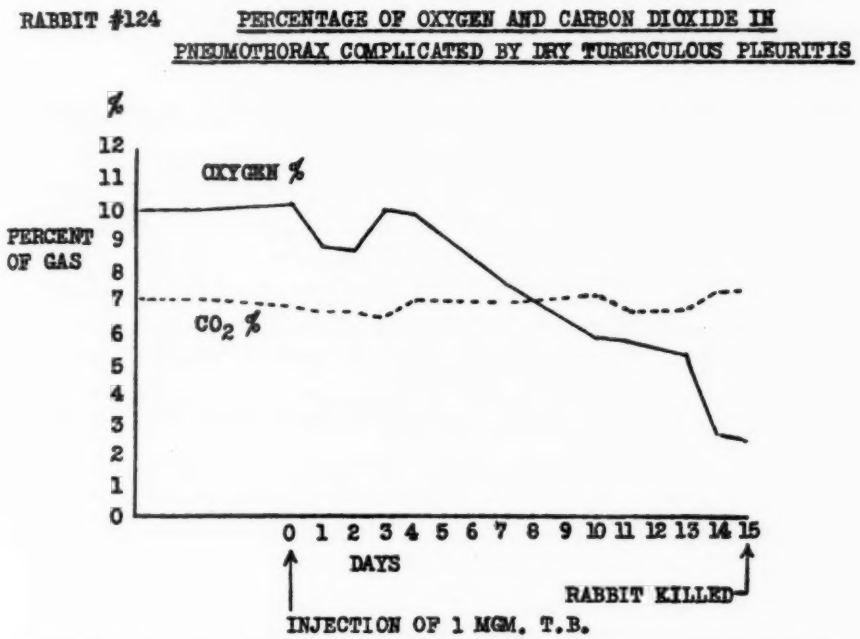

CHART 2. Percentage of oxygen and carbon dioxide in pneumothorax complicated by dry tuberculous pleuritis

the oxygen in solution in the pleural tissues is established in less than twenty-four hours.

In uncomplicated pneumoperitoneum in 4 rabbits the oxygen percentage varied between 5 and 7.5 per cent. Following the production of tuberculous peritonitis, the oxygen showed the same fall in value as it did in pneumothorax complicated by tuberculous pleuritis. This proves that the fall of oxygen values in the latter case is not due to interference with the aeration of the underlying lung.

In 3 rabbits we have induced artificial pneumothorax and then produced a marked thickening of the pleura by the use of the following

sterile irritants: olive oil, paraffin oil or repeated sprayings of talcum powder. There was very little or no change in the percentage of oxygen in the pneumothorax space following these experiments. For example, in one rabbit pneumothorax was induced and then 50 cc. of sterile paraffin oil were injected into the pleural sac and the pneumothorax was continued until the twenty-fifth day after the oil fill when the animal was killed. The oxygen percentage in the space varied between 7 and 8.5 per cent during the entire period. At necropsy there was a marked thickening of the pleura consisting of a fibrous tissue stroma, numerous

TABLE 1

Percentage of oxygen and carbon dioxide in uncomplicated pneumothorax in patients. Samples taken before intrapleural pneumonolysis

Number of patients—26

	OXYGEN	CARBON DIOXIDE
Highest percentage of oxygen and carbon dioxide	5.1	7.8
Lowest percentage of oxygen and carbon dioxide	1.9	5.7
Average percentage of oxygen and carbon dioxide	3.3	6.9

TABLE 2

Percentage of oxygen and carbon dioxide in pneumothorax complicated by tuberculous pleuritis with effusion

Number of cases—26. Pleural fluid positive for tubercle bacilli in 20 cases

	OXYGEN	CARBON DIOXIDE
Highest percentage of oxygen and carbon dioxide	0.6	13.6
Lowest percentage of oxygen and carbon dioxide	0.1	8.0
Average percentage of oxygen and carbon dioxide	0.3	11.2

large monocytes and blood capillaries. This indicates that the fall in oxygen values in pneumothorax complicated by tuberculous pleuritis cannot be explained on the basis of thickening of the pleura.

OBSERVATION ON PATIENTS

In an attempt to determine the percentage of oxygen and carbon dioxide in artificial pneumothorax not complicated by tuberculous pleuritis, samples were taken before the operation of intrapleural pneumonolysis. Table 1 shows the results in the cases in which our surgeon, Dr. Ross Robertson, could see no evidence through the thoracoscope of tuberculous foci in the pleura.

The oxygen percentage was, on the average, 1 per cent lower in cases in which one or more tuberculous foci were visible in the pleura. Cases with extensive tuberculous pleuritis had oxygen values of less than 1 per cent.

In table 2 are the percentages of the gases in pneumothorax complicated by tuberculous pleuritis with serous or purulent effusion in an amount which at least covered the diaphragm. It is apparent that, in patients with tuberculous pleuritis complicating the pneumothorax, the oxygen percentage falls to a low level similar to that observed in rabbits.

SUMMARY AND DISCUSSION

This is an experimental study in 30 rabbits of the changes in the percentage of oxygen in pneumothorax and pneumoperitoneum under a variety of conditions.

There is a marked fall in the percentage of oxygen in pneumothorax complicated by active tuberculous pleuritis with or without a pleural effusion. This fall in oxygen tension cannot be explained on the basis of thickening of or changes in the permeability of the pleural membrane for the following reasons: (*1*) Pneumothorax complicated by aseptic or sterile pleuritis was accompanied by little or no change in the percentage of oxygen. (*2*) Concurrent with the healing of tuberculous pleuritis in rabbits, the oxygen percentage gradually rose to 5 or higher. There was much more generalized thickening of the pleura of a fibrous tissue type in some of these rabbits than there was, for example, in the rabbit illustrated by chart 2, which had an active focal pleuritis, without effusion, and in which the oxygen percentage was down to 2.5. (*3*) In pneumothorax complicated by active tuberculous pleuritis the oxygen percentage, twenty-four hours or longer after a refill, was at the same low level irrespective of whether the refill gas was air, oxygen or nitrogen. This, we believe, indicates that the controlling factor was the mean tension of oxygen in solution in the pleural tissues; pressure equilibrium with the oxygen in solution in the pleural tissues is reëstablished within twenty-four hours after the refill. The fall in oxygen cannot be explained on the basis of interference with the aeration of the underlying lung because the same fall in oxygen values occurs in pneumoperitoneum complicated by tuberculous peritonitis. Therefore, we believe that the fall in oxygen values in pneumothorax complicated by active tuberculous pleuritis reflects a corresponding fall in the mean tension of oxygen in solution in the pleural tissues.

This is also a clinical study of the gases in artificial pneumothorax in patients with pulmonary tuberculosis. Pneumothorax complicated by tuberculous pleuritis is accompanied by a fall in the percentage of oxygen similar to that found in rabbits.

More than 900 samples of gas were analyzed during the investigation.

Some authors have attributed the low oxygen percentage in some cases of pneumothorax as being due to the blood supply to the pleura of poorly aerated blood from the atelectatic underlying lung. However, the blood supply to the pleura in man is, according to Miller (16), entirely from the systemic circulation; the supply to the visceral pleura comes from the bronchial artery.

One of the characteristics of the tuberculous granuloma is the relative scarcity of blood capillaries. Perhaps the low oxygen tension in active tuberculous tissues results from the combination of two factors, namely, the oxygen consumption by inflammatory cells and tubercle bacilli on the one hand, and the diminished oxygen supply because of the sparse blood capillaries on the other. However, the fall in oxygen may begin to appear as early as the second day after the introduction of the infection as illustrated by chart 1. Since specific tuberculous lesions are not formed before at least a week has elapsed, this early fall in oxygen values may be due to the consumption of oxygen by the acute inflammatory cells which make their appearance at that time.

Since the tubercle bacillus is a strict aerobe, the growth of which is progressively slower in the presence of decreasing oxygen concentrations (17, 18), the low oxygen in active tuberculous tissues may be an important factor in the resistance of the host to the tubercle bacillus.

Conversely, the author (19) has reported observations which indicate that a flare-up in tuberculous pleuritis may occur if the oxygen supply to the pleura is artificially increased.

CONCLUSIONS

1. There is a marked fall in the percentage of oxygen in pneumothorax complicated by active tuberculous pleuritis as compared with that in uncomplicated pneumothorax. This probably reflects a corresponding fall in the mean tension of oxygen in solution in the tuberculous pleural tissues.

2. Since the tubercle bacillus is a strict aerobe, the growth of which is progressively slower in the presence of decreasing oxygen concentrations,

this fall in oxygen percentage may be an important factor in the resistance of the host to the tuberculous infection.

We wish to express our indebtedness and gratitude to Dr. H. C. P. Hazlewood and the Board of Trustees of the Muskoka Hospital for having provided the facilities which made this work possible.

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ALLERGY AND IMMUNITY[1]

An Analysis of Their Interdependence

ERICH URBACH AND PHILIP M. GOTTLIEB

One of the basic problems of modern immunology is the relationship of immunity to allergy. The viewpoints on this subject can be divided into three schools of thought: (*1*) immunity is a special type of allergic hypersensitiveness, (*2*) immunity is a manifestation of allergic hyposensitiveness, and (*3*) immunity and allergy are distinct and unrelated processes. The last view, championed by Rich (1), has recently gained a considerable following.

The whole question has more than theoretical significance. If it were possible, for example, to abolish hypersensitiveness to tuberculin, at the same time leaving the immunity mechanism intact, the liability to an extensive necrotic and caseous form of tuberculosis would be greatly reduced.

As will be shown below, it is essential to define accurately the terms allergy, anaphylaxis and immunity, as they are to be used in the following discussion.

Allergy may be defined as an alteration in the reactivity of an organism, resulting from the production of specific antibodies after exposure to an exogenous or endogenous agent, called the antigen. Because of the altered reactivity, subsequent exposure to the same antigen will elicit a different response, usually more rapid and more intense.

By *anaphylaxis* we mean that form of allergic hypersensitiveness occurring in experimental animals and manifested by a constitutional reaction, the anaphylactic shock.

Immunity is a state of specific increased resistance to, or tolerance of, pathogenic agents and/or their products. This results in a complete or relative insensitiveness to the introduction of microörganisms and/or their toxins. Such a condition may be characteristic of a species or a race but can also be an innate quality of the individual. In the latter instance, if the immunity is due to inability to produce antibodies for bacteria, viruses, etc., it is called *natural anti-infectious immunity* or

[1] From the Jewish Hospital, service of Dr. Erich Urbach, Philadelphia, Pennsylvania.

better, *natural refractory state.* However, when the immunity is acquired, either actively, as a result of disease or vaccination, or passively, by transfer of antibodies, whether from the mother through the placenta or artificially by the injection of antiserum derived from an actively immunized animal or individual, it is termed *acquired anti-infectious immunity.*

Likewise, with regard to the toxic diseases, we speak of *natural antitoxic immunity* or preferably, *natural resistance to toxin,* and of *acquired antitoxic immunity.*

We shall here confine our attention to the acquired anti-infectious or the so-called *reinfection immunity.* This type is brought about by the production of a series of specific antibodies (for example, agglutinins, precipitins, opsonins, lysins, tropins, etc), which are formed in response to the infection.

Immunity against infectious agents is not a state of insensitiveness, as assumed by Rössle (2), but rather a state of hypersensitiveness to constituents and metabolic products of the bacteria. This is clearly shown by the high antibody-titre in the blood of immunized human beings and animals.

Various authors employ the terms allergy and immunity in rather different senses. We wish to emphasize from the start that the variety of interpretations given to the concept of allergy by the leading students in this field is the main reason for the difficulties involved in this problem. For instance, Rich (1) restricts the meaning of allergy to "that state of specific hypersensitivity which develops as a result of the entry of foreign protein into the tissues, and which manifests itself locally by the occurrence of tissue damage and inflammation wherever the foreign protein, or even a specific fraction of the sensitizing molecule (haptene) lodges in the previously sensitized tissues." According to Birkhaug (3), the term allergy, as regards tuberculosis, should be reserved for the essentially inflammatory and necrotizing local and focal reactions, as well as the intoxicating general reactions following soon after the injection of tuberculin or of large numbers of living or dead tubercle bacilli into a tuberculous organism.

These two investigators are the leaders of the school believing that tuberculin allergy and tuberculin immunity are distinct and dissociable phenomena. But they understand by allergy merely acquired cutaneous hypersensitiveness, that is, an increased reactivity of the skin to tuberculin in cases of tuberculosis. Rich, Birkhaug and their adherents

therefore exclude specific acquired immunity from the realm of allergy; although it has always been regarded, since Pirquet's time, as one of the cardinal manifestations of allergy.

We hope to demonstrate from precisely the experimental findings of Rich and his followers (4) that their conclusions would be entirely tenable, if they restricted themselves to the statement: Allergic tuberculin hypersensitiveness and acquired resistance to tuberculosis are distinct and dissociable phenomena. However, when they infer that allergy is not necessary to the operation of immunity, it is, as will be shown below, an unwarranted and misleading conclusion.

In a series of highly interesting and important contributions, Rich (4, 5) and his collaborators have arrived at the following conclusions:

1. *That immunity can be dissociated from allergy by three methods:*

   (a) *The establishment of acquired immunity without the concomitant development of allergy:* Rich inoculated the testes of animals with spirochetes from human chancres. When the immunized animals were reinfected with large numbers of virulent spirochetes, the acquired immunity was manifest not by the expected allergic inflammation at the site, but instead by a remarkable indifference of the tissues to the presence of the injected organisms. The site of reinfection remained practically normal and no distant lesions developed. In non-immune controls, on the other hand, a large local chancre and lesions in remote tissues regularly ensued.

   (b) *The passive transfer of immunity without transfer of allergy:* Normal animals were given serum from animals that were immune and allergic to the pneumococcus. When they were then infected with virulent pneumococci, it was found that no allergic reaction of any sort occurred, although a strong immunity was present.

   (c) *The persistence of immunity after abolition of allergy by desensitization:* Rabbits were rendered allergic and immune by intracutaneous injections of bacterial vaccine. Half the animals were then desensitized by intravenous administration of large amounts of the same vaccine. All of them, along with normal controls, were then infected intracutaneously with virulent organisms. It was found that, although the desensitized group of animals showed no allergic reaction whatever, they were as completely immune to a multiple

of lethal doses as were the allergic ones which developed a severe inflammation. Similar desensitization experiments in tuberculous infection by Rothschild, Friedenwald and Bernstein (7) yielded the same results.

2. *That inhibition of the spread of bacteria in the immune body is not dependent upon allergic inflammation, as has been generally assumed, but is effected primarily by the action of immune antibodies:* Histological examination of the lesions in the normal control group of animals showed a rapid dissemination of pneumococci through the tissues, while in both the allergic and immune and the desensitized and immune groups, the bacteria remained localized in agglutinated clumps. According to Rich, this observation lends further confirmation to the opinion that immunity operates irrespective of the complete abolition of allergy.
3. *That allergy can be established without immunity; acting alone, it lowers resistance to infection:* In a series of thorough studies, Birkhaug (8) has confirmed these ideas, especially in tuberculosis. He presents experiments supporting the contention that the allergic state is unnecessary for protection in tuberculosis and that abolition of the hypersensitive state by tuberculin desensitization leaves the immunity intact. He also states that, in animals previously uninfected and therefore in the normal anergic state, tubercle bacilli will invade the entire body in less than three days. In animals rendered highly allergic to tuberculin by injections of bovine tubercle bacilli and then superinfected with human tubercle bacilli, there was a delay of approximately five weeks before the latter completely traversed the body. If such highly allergized animals were completely desensitized by tuberculin before and after they were superinfected, the spread of the bacilli was delayed to about seven weeks.

Rich's principle, "When the tuberculin hypersensitivity of an experimental animal is abolished by desensitization, the immunity remains intact," has been corroborated by many other investigators (Birkhaug (3, 8), Corper, Cohen and Damerow (9), Pagel (10), Bieling and Oelrichs (11), Siegl (12), Selter and Wieland). Thomas and Duran-Reynals (13) found that the rabbit, although exhibiting little skin hypersensitiveness to tuberculin, has marked resistance to superinfection; while the guinea pig, in spite of marked skin reactivity, has relatively little tissue immunity. The discrepancy between immunity and allergy has also been

shown to exist in the case of other microörganisms. Angevine (14) showed that rabbits evidence considerable skin sensitivity but scant immunity to hypodermic injections of relatively avirulent cultures of haemolytic streptococcus; on the other hand, when a culture made more virulent by animal passage was used, little skin sensitivity but marked immunity resulted.

Furthermore, clinical experience has shown that skin allergy in man fluctuates widely in tuberculous individuals and is in no way related to the clinical outcome.

Although these experimental and clinical observations are unquestionably acceptable, the conclusions reached by Rich and his followers have become extraordinarily controversial.

We may now present the experimental evidence favoring the opposite idea, that immunity, anaphylaxis and cutaneous hypersensitiveness are to be properly regarded as merely quantitatively different types of reactions, all based on the same fundamental mechanism—allergy.

Metalnikow (15) sensitized guinea pigs with killed cholera vibrios. These animals were then able to tolerate without reaction the subcutaneous administration of a dose of living cholera vibrios lethal for nonsensitized animals. This is, of course, an example of immunity.

To demonstrate that the same animals are anaphylactic under different experimental conditions, Metalnikow administered large doses of vibrios subcutaneously or small doses intravenously. This always resulted in anaphylactic death. This means that the administration of a bacterial antigen produced at the same time a state of resistance and of hypersensitiveness to the antigen. The type of reaction depends on the size of the second dose: small amounts induce an immune reaction, which protects the organism, while larger ones produce a severe, often fatal shock. Metalnikow correctly concluded from these experiments that immunity and anaphylaxis are two reaction-types of the same state of hypersensitiveness resulting from the injections of the antigen.

Hamburger (16) made similar observations in tuberculous guinea pigs, with the results shown in table 1.

Table 1 explains the seemingly insurmountable discrepancy between Bail's and Koch's experiments on immunity. Bail showed that the intraperitoneal injection of large doses of tubercle bacilli (10 to 100 mg.) in tuberculous guinea pigs produced almost instantaneous death in anaphylactic shock. On the other hand, in nontuberculous guinea pigs there generally were no signs of disease in the first days following infection. On the contrary, under the conditions employed by Koch in his

historic experiments, a not inconsiderable degree of immunity to small doses of tubercle bacilli resulted. Moreover, as Römer and Hamburger have demonstrated, complete immunity can be established by reinfection with very small doses; that is, while a primary tuberculous complex appears in control animals three to four weeks after the infection, tuberculous animals usually reveal no further pathological changes on reinfection. Thus the behavior of the tuberculous animal depends on whether very large or very small doses are employed for the reinfection.

Likewise, Bronfenbrenner (17) concluded on the basis of carefully conducted experiments that every immune animal will respond with the symptoms of hypersensitiveness if the antigen is introduced under suitable conditions designed to elicit this type of response.

All these factors prove that hypersensitiveness and acquired anti-infectious immunity are varying expressions of an identical biological

TABLE 1

	TUBERCULOUS GUINEA PIG	NORMAL GUINEA PIG
Reinfection with 100 mg. of tubercle bacilli (intravenously)	Dies within several hours. ("Anaphylaxis")	Remains well for days, becomes sick only after a week.
Reinfection with very small dose (intracutaneously)	No change in condition. ("Immunity")	After two to three weeks, evidences primary complex of tuberculosis.

process, namely, allergy. They can be reproduced at will, provided that certain definite experimental conditions be maintained (particularly the quantity and route of administration of the antigen).

It may be pointed out that the experimental findings of Metalnikow, Hamburger and Bronfenbrenner in no way contradict those of Rich, Birkhaug and their school. All these experiments clearly prove two facts: (*1*) that the results are completely dependent on the dose of tuberculin, the duration of tuberculin treatment, the dose of bacilli, the time of reinfection in relation to the beginning of desensitization, and other experimental conditions (Woodruff and Willis (18), Clayson (19)); (*2*) that the whole controversy hinges on this crucial point: just what are we to understand by allergy?

Most of the disagreement is due to the fact that Rich tends to narrow his concept of allergy to the point of having allergy signify, almost exclusively, the acquired hypersensitiveness of the skin.

Schick (28), the distinguished collaborator of Pirquet, charges: "Rich

identified hyperergic reaction with the whole of allergy." The fact that Rich was able to abolish skin sensitiveness without eliminating the manifestations of increased resistance demonstrates only that skin sensitiveness is but one part of the phenomena of allergy; just as the anaphylactic reaction or the hypersensitiveness following smallpox vaccination constitute only a very small part of the totality of allergy. To-day, the overwhelming majority of all investigators in immunology and allergy (Zinsser, Topley and Wilson, Kolmer, Vaughan, Tuft, Doerr, etc.) share the opinion that every instance of altered reactivity which is based on an antigen-antibody reaction must be considered as allergic. In this category, therefore, also falls immunity to reinfection, and it is self-evident that not only the allergic and immune, but also the desensitized and immune groups are to be included here. This last designation was employed by Rich for those animals in which the cutaneous hypersensitiveness—called allergy by Rich—had been abolished by desensitization, but in which resistance to infection remained intact.

The altered reactivity which underlies the immunity of the desensitized and immune group is revealed not only in clinical and histological observations, but also in serological investigations. Thus, tuberculous-allergic guinea pigs after desensitization with tuberculin still have positive complement-fixation reactions, according to Higginbotham (20). Likewise, Freund, Laidlaw and Mansfield (21) showed that, when sensitiveness in rabbits disappeared as tuberculosis progressed, there was no decrease in complement-fixing antibodies.

From these experiments it is apparent that the desensitizing treatment does not destroy the antibody content of the serum. This, however, is certainly not to be expected, since, in the opinion of the majority of all immunologists, the desensitization method does not give rise to a true desensitization, which would lead to a loss of antibodies. On the contrary, all the desensitizing methods are followed by an increase in the antibody content of the blood.[2] This increase in antibodies and consequently the protective immunity persists only so long as the administration of the antigen (for example, tuberculin) is continued. This fact has been experimentally proved in both human beings and animals. Thus, by rapidly increasing the daily dose of tuberculin, Hamburger (16) obtained a state of nonreactivity to 100,000 times the size of the dose which was originally sufficient to elicit a reaction in 10 children with

[2] De-allergization, by which we mean those methods which lead to neutralization or loss of cellular antibodies, cannot be achieved in infectious allergies (Urbach (22)).

surgical tuberculosis. This means that within a period of six weeks all the patients could be rendered tolerant to a dose of 100 mg. of tuberculin, whereas previously they reacted to 0.001 mg. This relative insensitiveness, however, persisted only two to three weeks after the discontinuance of the injections. Rich (1) has apparently made similar observations in animals, for he states: "It is not enough merely to achieve desensitization; it must be maintained continuously for a period of time long enough to permit the forces of immunity to act without being thwarted by the recurrence of tissue hypersusceptibility." The investigations of Willis and Woodruff (23, 24), however, have shown that even a long-continued desensitization of the animal did not produce the desired result. These authors, instead of finally sacrificing their animals as did Rothschild and his collaborators (7), allowed them to die from the infection. In comparison with the allergic and immune animals, the desensitized and immune guinea pigs lost a considerable degree of the protection they had acquired from their primary infection. While 45 to 75 per cent of the former were still alive in the sixth month after being infected, all the latter were dead by this time. Normal desensitized animals (guinea pigs never permitted to become allergic by means of large doses of tuberculin from the very beginning of the infection) succumbed to tuberculosis even before the normal controls. Histological study of the lungs of the desensitized and immune guinea pigs revealed that the organs were far more extensively diseased than in the allergic and immune animals, and also contained many acid-fast bacilli.

Siegl (12) compared desensitized and immune tuberculous animals, in which the injections of tuberculin (1,000 mg. per dose) were stopped on the day before reinfection with those in which the desensitization was continued even after reinfection. He was able to show that the first group survived approximately one and one-half months longer. The unfavorable effect of prolonged large dosage of tuberculin is also recognized in tuberculous human beings. It is accompanied, as is well known, by a diminution of cutaneous hypersensitiveness, designated as negative or cachectic anergy. Rich has not seen the undesirable influence of long-continued large doses of tuberculin in his experimental animals, apparently because, as Siegl indicates, he did not use tuberculous animals, but rather those which had been infected with attenuated bacilli. This type of infection scarcely occurs in human beings.

The animal researches of Willis and Woodruff and of Siegl show that it is still quite doubtful whether, in the final analysis, a state of desensitization and immunity is preferable to one of allergy and immunity.

Regarding the treatment of human tuberculosis, there are similarly two diametrically opposite viewpoints: one, represented by Calmette and his associates, favors the attempt to produce artificially a condition of allergy to tuberculoprotein; the other, represented by Rich and his school, holds that allergy is injurious to the tuberculous organism and that every effort should be made to abolish an allergic state. Rich recommends, therefore, that tuberculin therapy be carried out so energetically that complete desensitization will result. The question therefore arises: Is a state of hypersensitiveness essential for immunity? Rich maintains, "There has never been one single experiment or observation placed on record, through which hypersensitivity has been shown to be necessary for protection in any stage of any infection under any condition whatsoever." Woodruff and Willis reply, "While no unequivocal proof has been adduced that allergy is essential to protection, the fact remains that in such diseases as tuberculosis and smallpox protection has never been conferred, either experimentally or in the clinic, without first producing the hypersensitive state."

Finally, it may be of interest to consider the stand taken by those students who, while they have accepted the experimental results of Rich and his school, do not agree with his conclusions. Thus, according to Bieling and Oelrichs (11), only one important fact stands out from these experiments, namely, that the development of immunity is not associated with a hyperergic tissue reaction. Pinner (25) is therefore right, and this appears to us to be one of the chief results of this scientific controversy, in warning the clinician not to attempt to correlate a strong tuberculin reaction with a high degree of immunity, or *vice versa*. "Hypersensitivity [of the skin] is not an index of immunity." Siegl (12) concludes that tuberculin hypersensitiveness and immunity to reinfection are two coexisting manifestations, both resulting from an allergy produced by the primary infection. Hyposensitization treatment with increasing doses of tuberculin serves to suppress only one form of allergic reaction, the tuberculin hypersensitiveness, while the second form, the immunity, is preserved. Saenz (26) corroborated the finding of others than the sensitivity of the desensitized animal recurs relatively rapidly after reinfection; he considers this as evidence for the fact that some degree of allergy persists even after complete desensitization of the skin.

Kallós (27) raises the interesting question whether the specific nonreactivity of the skin in a patient with bacterial infection is an expression of a positive anergy. This refers to the well known fact that in infectious

diseases, such as tuberculosis, patients in very good physical condition may show an incapacity to react cutaneously to tuberculin. As is now recognized by many investigators, the skin of these patients contains specific antisubstances, the so-called anticutins.

Bronfenbrenner (17) is of the opinion that the phenomena of experimental anaphylaxis, of clinical hypersensitiveness and of specific acquired resistance to infection are all the result of a single underlying mechanism, and that the character of the entire observable reaction is determined by secondary factors.

We may now summarize our own position in the following four points: (*1*) Reinfection immunity can never occur without a preceding infectious allergy. (*2*) Even if the ability of a previously infected organism to react to superinfection with inflammatory exudative manifestations is lost or depressed, still the body cannot entirely return to its former state of reactivity. At least a subclinical or latent allergy will remain. (*3*) Even the fact that the local inflammatory reaction of the skin to tuberculin can be suppressed without affecting the degree of the animal's specific resistance, in no way proves that the two phenomena are independent of each other. This is so because hypersensitiveness of the skin represents only one form of allergy and not allergy itself. (*4*) Rich's experiments convincingly prove that cutaneous hypersensitivensss (characterized by oedema, inflammation and tissue destruction) is not necessary for the existence of immunity; those of Willis and Woodruff, and of Siegl, however, show that an altered reactivity must be present in order that the immunity remain operative.

SUMMARY

Whether immunity is based on allergy, or whether they are distinct and unrelated processes is a problem of major practical and theoretical importance. The answer to this question depends on whether allergy is taken to mean the altered reactivity of the organism (in the original meaning of Pirquet) or only the acquired hypersensitiveness of the skin (as considered by Rich). We adhere to the former, more embracing concept. On the basis of the experimental results cited, we hold that immunity to reinfection, experimental anaphylaxis and clinical hypersensitiveness represent only special types of allergy. Rich's work proves that cutaneous hypersensitiveness is not necessary for immunity to reinfection. Nevertheless, it cannot negate the fact that an altered reactivity is an indispensable prerequisite for reinfection immunity.

Rich's valuable investigations, however, have clarified the important point that skin hypersensitiveness, in infectious diseases, is not an index or measure of immunity.

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THE INSPISSATED CAVITY[1,2]

ARNOLD SHAMASKIN

Considerable diversity of opinion exists regarding the significance and implications of the blocked inspissated cavity, the course it may follow and the treatment to be applied. This lack of unanimity is due, in considerable measure, to the scarcity of suitable pathological material. Since the nature of the process is one of healing, as this report will attempt to show, the inspissated cavity is rarely encountered in the usual autopsy material of tuberculosis institutions. The report made by Auerbach and Green (1) on the pathology of clinically healed tuberculous cavities is, therefore, of particular interest because it is based on material collected from autopsies where death was not due to progressive pulmonary tuberculosis. Their conclusions are corroborated by the clinical and roentgenological observations recorded in this presentation.

The tuberculous cavity was very aptly referred to by Mayer (2) as one of the "paradoxes" in that "it destroys as it heals." Indeed it indicates, under certain conditions, a degree of resistance to the invading organism and signifies, in a measure, a victory on the part of the host. It is, however, a Pyrrhic victory, since it is both a victory and a defeat; a victory immunologically and a defeat anatomically and epidemiologically.

Much has been written concerning the healing of tuberculous cavities, yet this perplexing problem is far from solved. The difficulty frequently lies in the attempt to embrace too wide a field and to explain the closure of all cavities on the basis of one theory; whereas the mechanism of cavity closure is, probably, different under different conditions. The closure of the draining bronchus is, undoubtedly, a factor in the obliteration of some cavities, but the consensus does not attribute to it the importance Coryllos did (3). In fact it may, at times, be responsible for preventing cavity obliteration as illustrated by one of our cases (case 1, figures 1, 2 and 3).

[1] From the Veterans Administration, Oteen, North Carolina.

[2] This paper is published with the permission of the Medical Director, United States Veterans Administration, who assumes no responsibility for the opinions expressed or conclusions drawn by the author.

Salkin, Cadden and McIndoe (4) have shown that a cavity can exist without communication with the tracheobronchial tree, that it may, while in this state, behave like any other cavity, and may alternately become filled with debris and empty, giving an X-ray appearance at one time of a dense shadow and at another time an area of rarefaction. They attribute the latter phenomenon not, necessarily, to the opening and closing of the draining bronchus, but to the ability of air and fluid to pass through the cavity wall in either direction.

Auerbach and Green (1) in a pathological study of over 2,000 cavities have never seen an open cavity with a diameter of 3.0 cm. or more in which they were not able to trace a bronchus opening into the lumen of the cavity. They ascribe the discrepancy between their findings and those of the other group to the latter's inadequate search for an open bronchus.

Veterans Administration beneficiaries who carry a disability for pulmonary tuberculosis are followed up indefinitely with complete periodic examinations including roentgen studies of the chest. This system and the ample bed capacity usually prevailing in Veterans Hospitals, coupled with a liberal policy of admission and readmission for emergency or observation, and a flexibility of service in the types of cases admitted, provides opportunities for clinical observation not usually available elsewhere. Thus a number of patients having blocked inspissated cavities, some of whom were not in need of institutional care, came under the observation of the author. Six of these are presented below. The clinical and roentgenological data of some of these cases are available over a long period of time and their changes are of such nature that their presentation may help to shed light on the evolution, character, behavior and the ultimate fate of this type of lesion.

CASE REPORTS

Case 1: H. A. S., 32738, white, male, age forty-three. History dates back to 1927, when tuberculosis was diagnosed by X-ray and sputum examination and the lesion, according to the patient, was located in the left upper lobe. Since then he had one period of treatment of fifteen months' duration in 1927–1928, and one of eighteen months in 1931–32. The rest of the time he was gainfully employed. Temperature was always normal, sputum occasionally positive up to 1932, negative since then with one exception. He first came under observation of this facility in 1937, for a fractured patella. A routine chest X-ray film (figure 1) revealed a healed lesion in the left upper lobe. The most con-

spicuous roentgen shadow here was a homogeneous circular area of increased density, 4 cm. in diameter, sharply demarcated and situated behind the second left rib. In the immediate vicinity of this shadow there were several sharply outlined areas of fibrosis and calcification. The rest of the left lung as well as the opposite lung were clear. He was discharged after thirty-two days, not being in need of institutional care. He was readmitted to this facility September, 1939 with a partial right pneumothorax and a small amount of fluid on a shelf in the right pleural space. The pneumothorax was induced according to patient four months earlier for an acute pneumonic condition in the right lower lobe. No abnormal shadows were visible in the parenchyma of the right lung. The shadows in the left upper lobe were the same as on the previous film. The patient was afebrile, ambulant and his sputum negative for tubercle bacilli. A roentgenogram dated April 4, 1940 showed no significant changes. A routine X-ray film taken June 19, 1940 (figure 2) showed a fluid level in the previously homogeneous shadow in the left upper lobe. On an X-ray film taken September 13, 1940 (figure 3) the fluid level had disappeared and the homogeneous shadow was replaced by a very faint ring. On a roentgenogram made January 21, 1941 this ring is no longer perceptible. Pulmonary markings are visible all over. One out of 22 sputum examinations made at this hospital was found positive for tubercle bacilli and this one did not coincide with the appearance of the fluid level. At present this patient is ambulant, symptom-

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FIG. 1. Case 1. May 17, 1937. A homogeneous, sharply outlined density suggestive of an inspissated cavity in left upper lobe. Healed lesion in the vicinity. Rest of lung clear. Linear markings extend from lower pole to hilum.

FIG 2. Case 1. June 19, 1940. Fluid level in place of homogeneous shadow in left upper lobe. Otherwise X-ray findings essentially the same.

FIG. 3. Case 1. September 13, 1940. Fluid level disappeared. A very faint ring left in place of homogeneous shadow.

FIG. 4. Case 2. June 6, 1936. A homogeneous sharply outlined density suggestive of an inspissated cavity in left upper lobe. Evidence of a healed tuberculous lesion at the base. Linear markings from lower pole to hilum. Rest of both lungs clear.

FIG. 5. Case 3. April 3, 1936. Area of infiltration with hazy edges in right lower lobe. Cavity in the area of infiltration.

FIG. 6. Case 3. October 5, 1937. A homogeneous sharply outlined shadow in place of the cavity. Lung around it clear.

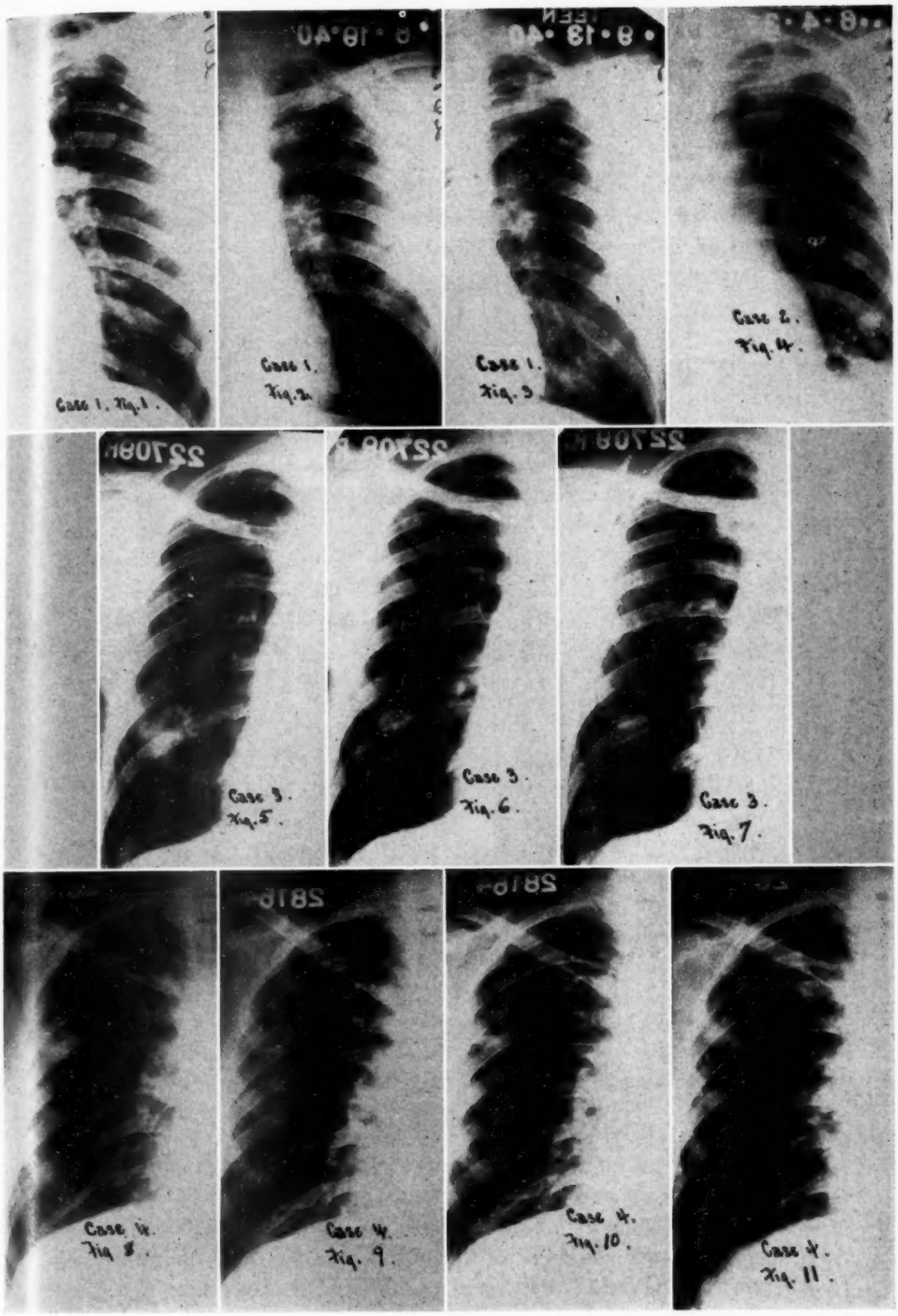
FIG. 7. Case 3. December 3, 1940. Resolution of the lesion, seen on previous film, is taking place.

FIG. 8. Case 4. July 21, 1938. Cavity with a very fuzzy wall partly behind the third right rib. Some infiltration in the immediate vicinity.

FIG. 9. Case 4. October 27, 1939. Cavity in the right lung looks punched out. Cavity walls sharper. Lung in the vicinity clearing.

FIG. 10. Case 4. April 11, 1940. Fluid level now visible in the cavity behind the third right rib. Lung in the immediate vicinity still clearing.

FIG. 11. Case 4. November 6, 1940. A homogeneous, sharply outlined shadow now visible in right lung in place of the cavity.


Case 1. Fig. 1.
Case 1. Fig. 2.
Case 1. Fig. 3.
Case 2. Fig. 4.
Case 3. Fig. 5.
Case 3. Fig. 6.
Case 3. Fig. 7.
Case 4. Fig. 8.
Case 4. Fig. 9.
Case 4. Fig. 10.
Case 4. Fig. 11.

FIGS. 1–11

less, sputum-negative and his pneumothorax has been discontinued. The right lung has almost completely reëxpanded and is free of parenchymal disease. Roentgenograms taken between 1927 and 1937 were not available, but a report of an X-ray examination made by a private roentgenologist, August, 1932, describes a shadow in the left upper lobe which fits in every detail the shadow seen on admission to this facility; thus extending the existence of this shadow, in the same form, over a period of at least eight years.

Comment: A shadow bearing all the earmarks of a blocked inspissated cavity is seen in the left upper lobe. After existing in this state at least eight years the cavity emptied and is now apparently completely obliterated. The patient has been in excellent condition during the entire known period of blockage with the exception of an acute febrile episode of three weeks' duration, accounted for by a pneumonic condition in the right lower lobe.

One can visualize in this case the gradual thinning of the cavity wall by either liquefaction or absorption of the specific tuberculous tissue, or by both, within the cavity and by resolution of the perifocal inflammatory exudate outside the cavity. By this process the cavity wall was reduced to a thin fibrous capsule serving as a line of demarcation between the inspissated cavity contents and the surrounding normal lung tissue. Thus, when this cavity opened and discharged its contents, there remained only a thin fibrous capsule as a cavity wall which soon collapsed. Persistence of the barely visible trace of the fibrous ring can be explained by an anteroposterior collapse of the cavity. The cavity blockage and its emptying were not accompanied by any special clinical manifestations nor positive sputum.

Case 2: F. K. N., 34162, white, male, age forty-four. He dates his tuberculosis since 1921. He first came under observation of this facility as an outpatient in June, 1936. A roentgenogram taken at that time (figure 4) shows a homogeneous, sharply demarcated oval shadow 3.5 x 5 cm. behind and below the first left rib. Linear markings extend from the lower pole to the hilum. Scattered through this lung and particularly at the base, are small areas of calcification and fibrosis. The right lung is clear. Roentgenograms taken prior to January, 1936 were not available. The patient was admitted to this facility October 14, 1940, for observation for activity. X-ray findings were exactly the same as those found four years earlier. He reacted normally to exercise, sputum remained negative for tubercle bacilli on numerous examinations. He was discharged after sixty days as inactive and not in need of institutional care.

Comment: The shadows in the left lung are the vestiges of a tuberculous lesion which healed by calcification, fibrosis and cavity inspissation. The history and the appearance of the roentgen shadows suggest that the lesion had existed in the present form for many years and could be considered healed.

Case 3: W. L. J., 34347, white, male, age thirty-two. History dates back to June, 1931, when tuberculosis was diagnosed. He entered a government hospital and remained there almost three years. He left the hospital of his own accord June, 1934. He first came under observation of this facility January, 1935. A roentgenogram taken at that time showed irregular linear markings in the right lower lobe, which were not recognized as evidence of tuberculosis. A diagnosis of pulmonary tuberculosis was later made on the basis of two positive sputa. He left the hospital of his own accord June 1, 1935. His temperature was normal throughout. He was readmitted April 2, 1936. A film dated April 3, 1936 (fig. 5) shows an area of infiltration in the right lower lobe. In the centre of this area is a 2 cm. cavity located in front of the ninth rib. The edges are very hazy. The rest of the right lung and the entire left lung are clear. Sputum is positive; temperature is normal. Pneumothorax was declined by patient. He remained in the hospital fifty-three days and left of his own accord. Between May, 1936 and December, 1940 he had two periods of hospitalization of eighteen days each. A roentgen examination made October 5, 1937 (figure 6) shows a homogeneous area of increased density 3 cm. in diameter, very sharply outlined and situated in front of the ninth rib, where the cavity was previously visible. The rest of the right lung in the vicinity has almost entirely cleared up and the remainder of this lung, as well as the opposite lung, is clear. Temperature is normal. Twelve sputum examinations were negative for tubercle bacilli at this time. A roentgenogram made December 3, 1940 (figure 7) shows the shadow previously visible in front of the ninth rib reduced from 3 cm. to 1.5 cm., still sharply outlined but less dense and triangular in shape. Linear markings are seen running from the shadow to the hilum. The rest of this lung and the opposite lung are clear. Temperature was normal throughout, his sputum was negative for tubercle bacilli on 13 examinations. He was discharged December 20, 1940 as not requiring any treatment.

Comment: This series of X-ray films shows clearly the evolution of a blocked inspissated cavity. The clearing of the lung around it and the sharp outline of the shadow are unmistakable evidence that the process is one of healing. This is confirmed by the clinical picture and by the disappearance of tubercle bacilli from the sputum. The last roentgenogram also shows that the eventual fate of an inspissated cavity can be resolution.

Case 4: W. H. B., 34253, white, male, age forty-seven. He dates his tuberculosis to a few days before his first admission to this facility on April 2, 1938. A roentgenogram taken April 4, 1938 shows a 3.5 cm. area of increased density with very hazy edges and beginning cavitation in the centre, situated in outer zone of the second right anterior interspace. There is considerable infiltration around it extending from the second to the fifth ribs anteriorly over the entire width of the lung field. The left lung shows infiltration throughout. A roentgenogram dated July 21, 1938 (figure 8) shows a 3 x 4 cm. cavity in the centre of the shadow behind the third rib. The lung around it is clearing. A film made October 27, 1939 (figure 9) shows the cavity behind the third rib, circular, sharply demarcated with a clear centre. The lung around it is still clearing. A sharply demarcated area of density 1 cm. in diameter is seen below the cavity. Beginning excavation is seen in the opposite lung. A film dated April 11, 1940 (figure 10) shows the walls of the cavity behind the third right rib thinner and there is a fluid level in the cavity. The smaller shadow below is thinning out. Cavitation is progressing in the left lung. The patient left the institution of his own accord on April 24, 1940. He was readmitted seven months later, November 5, 1940. A roentgenogram dated November 6, 1940 (figure 11) shows the cavity previously seen behind the third right rib, replaced by a dense, homogeneous, sharply outlined, almost circular shadow 3 x 3.5 cm. in diameter. Linear markings are extending from the lower pole of the shadow towards the hilum. The smaller density has almost disappeared. The rest of the right lung is fairly clear. Progressive excavation is taking place in the left lung. The patient runs a subfebrile course with positive sputum and his general condition is worse.

Comment: This series of roentgenograms shows the evolution of a blocked inspissated cavity. The gradual clearing of the lung around it and the sharp outline of the shadow suggests a process of healing. In this case inspissation of the cavity in the right lung and clearing around it seems to be taking place coincidentally with progression in the contralateral lung. It is, however, well known that retrogression in one lung and simultaneous progression in the other lung is not an uncommon occurrence.

Case 5: J. P., 34290, white, male, age fifty-one. He first came under observation of this facility October 22, 1937, giving a history which dated back about one and a half years. A roentgenogram made October 23, 1937, shows a punched-out cavity 3.5 cm. in diameter with a fluid level, situated behind the first left rib. The outline is very hazy. Considerable infiltration is seen around the cavity down to the third rib. Temperature is normal with an

occasional rise to 99.6°F. His sputum is positive. Pneumothorax was refused by patient. He left the hospital of his own accord January 1, 1938, after a stay of seventy-one days. He remained at home about three and a half years and returned to this facility November 12, 1940. An X-ray film dated November 1, 1940 shows the cavity behind the first rib replaced by a dense, homogeneous, sharply circumscribed shadow 3 cm. in diameter. The lung in the immediate vicinity is much clearer than before. There is a more recent area of infiltration, hazy in outline with, probably, beginning cavitation situated in the middle third of the left lung near the hilum and also in the right apex. The patient is afebrile.

Comment: This series of roentgenograms illustrates the development of a blocked cavity. The sharp outline and the clearing of the lung in the immediate vicinity of the dense shadow suggest a healing process. The present positive sputum can be accounted for by the more recent infiltration in the mid-zone of the left lung and in the apex of the right lung. There is nothing in the history or clinical picture which would suggest the symptom complex indicative of sputum retention.

Case 6: T. E. R., 31797, white, male, age forty-one. History dates back to 1925. He was admitted to this facility October, 1925, and discharged on completion of treatment June, 1927. An X-ray film taken on discharge showed a fibrous lesion in the apex of the right lung. No cavity was visible at any time. Temperature was normal throughout and sputum negative for tubercle bacilli on all examinations. After discharge he felt well, in so far as his lungs were concerned, and was employed most of the time over a period of eleven and a half years. He was readmitted to this facility January, 1939. A roentgenogram made January 10, 1939 shows a 2 x 3.5 cm. cavity in the right apex and infiltration extending down to the third rib. Remainder of the right lung and the left lung are clear. Temperature was normal and sputum positive for tubercle bacilli. Pneumothorax was induced February, 1939 and discontinued August, 1939, as ineffective. An X-ray film dated February 15, 1939 shows an ineffective pneumothorax and the cavity in the right apex partly filled. An X-ray film dated August 29, 1939 shows the cavity empty again. Sputum was positive for tubercle bacilli at this time. On an X-ray film made October 24, 1939 the right diaphragm is shown elevated due to a phrenicotomy and the cavity is closed again. A film dated September 16, 1940 shows the cavity open again. Meanwhile a gradual absorption of the infiltrate was noted in the right upper lobe below the clavicle on all X-ray films. The rest of the right lung, as well as the left lung, remained clear and sputum was positive. The patient was afebrile throughout. A partial thoracoplasty was performed followed by an uneventful recovery and conversion of sputum.

Comment: The cavity in this case closed and opened several times with alternate positive and negative sputum. At the same time retrogression has taken place in the rest of the lesion around the cavity. No symptoms suggestive of sputum retention were ever noted. Partial thoracoplasty was the treatment of choice.

DIAGNOSTIC CRITERIA FOR INSPISSATED CAVITY

The only conclusive proof of a blocked inspissated cavity is a series of roentgenograms in which an area of decreased density in an earlier film is seen in a subsequent film to contain a fluid level and still later to be replaced by a homogeneous density occuping the same anatomical area of the lung field (case 4). If the changes occur in the reverse order the proof is not as conclusive, since the shadow may have been a caseous bronchopneumonic focus which has become excavated. On the other hand, there may be only one roentgenogram available showing a homogeneous shadow which may or may not be an inspissated cavity (case 2). If that be the case, what, if any, may be the distinguishing characteristics of an inspissated cavity?

A glance at the shadow which represents a well established inspissated cavity strikes one as unusual and an analysis of the X-ray films of the cases covered by this study reveal certain prevailing common features which might serve as diagnostic guides.

An inspissated cavity appears on the X-ray film as a tennis-racquet shaped or circular shadow of, more or less, homogeneous density which is quite sharply demarcated from the surrounding lung tissue. The lung in the immediate vicinity of the shadow is, as a rule, but not invariably, relatively clear or, at least, free from extensive progressive disease. This process of clearing in the surrounding lung tissue is demonstrated in serial roentgenograms of our cases. In trying to reconstruct mentally the pathogenesis of the inspissated cavity from the series of our X-ray films, one gains the impression that retrogression has taken place in the entire area of the lung involved. Where the disease has not progressed to cavity formation the lung cleared by resolution or fibrosis, while the cavity closed by bronchial occlusion and inspissation of its contents.

The density of the shadow produced by a cavity filled with debris will, naturally, vary with the length of its anteroposterior diameter and the character of its contents. It is usually of the same density as an area of caseous bronchopneumonia of the same dimensions. It may be expected that with the increased deposition of calcium salts the shadow will become denser.

Linear markings were traced in all our cases running from the pole of the inspissated cavity nearest the midline to the hilum of the lung. These linear markings represent, apparently, the draining bronchi. There were also found in most of our cases evidences of tuberculosis past or present in other parts of the lungs.

Coincidentally with the conversion of the area of decreased density into an area of increased density and the absorption of exudate around it, the clinical picture in all our cases was that of a state of retrogression or arrest, unless there was a progressive lesion elsewhere.

An inspissated cavity may be mistaken for an area of caseous bronchopneumonia. However, an area of caseous bronchopneumonia is not as sharply outlined, since it is more intimately connected with the surrounding lung tissue. The lung around the area of caseous bronchopneumonia is, as a rule, not as clear as around an inspissated cavity. While the latter represents apparently the end results of retrogression, the former is usually the seat of active disease.

The inspissated cavity, particularly when isolated, may also resemble a metastatic neoplasm (case 2). The latter is frequently multiple, there are usually evidences of the primary lesion elsewhere in the body, no connection with the bronchial tree can be seen and the lung is not, as a rule, the seat of an older tuberculous lesion. A benign neoplasm, a cyst or a chronic pulmonary abscess may be indistinguishable from an inspissated cavity. The history of the case may help in the diagnosis.

TREATMENT

The treatment of the inspissated cavity will depend upon its behavior and also upon the condition of the rest of the lung. Presuming there are no contraindications to any therapy elsewhere in the lung or that the inspissated cavity is the only visible significant lesion, what shall be our attitude towards it?

If the inspissated cavity shows a tendency to open and close alternately, it should, no doubt, be treated the same as any other cavity by collapse therapy. It would seem, however, that the cavity filled with debris due to the occlusion of the draining bronchus is less amenable to collapse therapy than an open cavity. According to our concept of the pathogenesis and mechanics of bronchial occlusion, many of these are complete and are produced by dense fibrosis and cicatrization, an obstruction which is not likely to be overcome by collapse therapy. Eloesser (7) found that, if the bronchi are not free, collapse therapy will only displace the cavity but will not collapse it. Coryllos (5) also found blocked cav-

ities refractory to collapse therapy. It is, therefore, best, when dealing with a cavity which opens and closes alternately, to institute collapse measures at the time the cavity is open, when the indications for such measures are more definite and satisfactory results are more likely.

The cavity presenting a somewhat puzzling problem is the one which has remained blocked and inspissated for a considerable time, while the rest of the lung is either clear or shows healed lesions and the patient presents no clinical or other evidences of activity. To what extent shall the treatment in such cases be influenced by the possibility that the cavity may open, even after a lapse of several years, and also by the reported finding of tubercle bacilli by Auerbach and Green (1) in such cavities on autopsy, where death was due to other causes than progressive pulmonary tuberculosis? In other words, shall we consider such cavities healed because they are not productive of bacilliferous sputum and regardless of the fact that tubercle bacilli may be locked in their contents?

On the surface the latter procedure would seem inconsistent. It is, however, known that viable tubercle bacilli may be locked for years in healed cicatrized tuberculous foci the same way they were shown to be held in blocked inspissated cavities. Endogenous reinfection with these bacilli is held responsible for the break-down and reactivation of many so-called arrested or healed cases of pulmonary tuberculosis and for the onset of most cases of reinfection tuberculosis (Fishberg (8)). If we do not hesitate to pronounce any case arrested while in possession of this knowledge, it is resonable to apply the same principle to inspissated cavities. Indeed, if we are to wait until we are reasonably sure no living tubercle bacilli are harbored anywhere by a patient we never could consider any case arrested.

The behavior of the cases presented tend to indicate that once blockage of the cavity and inspissation of contents has taken place this lesion would seem, from a clinical and therapeutic point of view, little different from an area of caseous bronchopneumonia of similar dimensions. If the inspissated cavity shows no tendency to reopen, the rest of the lung is either clear or shows healed lesions and the patient presents no clinical or other evidences of activity, it would be best to pursue a watchful policy. It would, however, be advisable to X-ray such a patient more frequently and to allow a considerably longer period of observation under the hardening process before pronouncing him an arrested case. Should the inspissated cavity show at any time a tendency to reopen, which may happen even after a lapse of years (case 1), collapse measures would then be in order.

COMMENT

The diagnostic criteria suggested for the identification of the inspissated cavity are based on the type of blocked cavities observed, 6 of which were presented. These criteria might help to distinguish the inspissated cavity from other conditions which may resemble it. There are, however, occasions when distinction is impossible and the only absolute proof of an inspissated cavity is then a series of roentgenograms as illustrated by some of the cases presented.

The roentgenographic appearances, the clinical pictures and the histories of the cases presented warrant the conclusion that cavity blockage and inspissation of contents are apparently a phase in a healing process, although it may not always be successful in accomplishing the purpose. The failure may be due either to the inability of the cavity to stay closed (case 6) or to a new or a progressive old lesion elsewhere in the lung (cases 4 and 5).

The cases presented also tend to demonstrate that there is no constant pattern to the course the inspissated cavity is apt to follow. It may remain permanently blocked and inspissated (case 2). It may open and close alternately (case 6). It may undergo resolution after closure and inspissation (case 3). It may open, empty its contents and then become obliterated by some other mechanism (case 1). Terplan (6) could not find any tubercle bacilli in bacterioscopic examinations of numerous calcified primary foci, although they are usually numerous in caseated foci. We may, therefore, suppose by analogy that tubercle bacilli may disappear eventually in inspissated cavities under similar conditions.

The treatment of an inspissated cavity will depend upon its course. An inspissated cavity in the presence of negative clinical and laboratory findings and of roentgen evidences of a retrogressing or healed lesion should be treated conservatively as a closed cavity.

The acute symptom-complex, occasionally encountered in cases of progressive pulmonary tuberculosis and characterized by sudden reduction or complete suppression of sputum accompanied by severe, dry cough, chest pains, marked elevation of temperature and other symptoms of toxemia, were never observed or recorded in the cases studied. Since these symptoms are evidently due to interference with the elimination of sputum and are relieved when the flow of sputum is reëstablished, it may be referred to as cavity blockage with sputum retention in contradistinction to cavity blockage with inspissation of contents.

Pinner (9) was correct in referring to the blocked cavity he had in mind

as a "grave clinical complication." However, in the writer's experience all blocked cavities which were shown on the roentgenograms as sharply demarcated homogeneous densities were never accompanied by the severe symptoms suggestive of sputum retention. The two types of blockage are evidently separate and distinct entities. The former is undoubtedly a clinical complication, while the latter is unmistakably part of a healing process as was shown by roentgenological and clinical evidences. The difference is, probably, due to the character of cavity contents.

SUMMARY

1. The significance of the inspissated cavity is discussed and cases are presented to illustrate the evolution, behavior and ultimate fate of this type of lesion.

2. Diagnostic criteria are suggested for the recognition of the inspissated cavity and its treatment is discussed.

3. Evidences are presented to show that cavity blockage with inspissation of contents is a beneficial process.

4. A distinction is made between cavity blockage with inspissation of contents and cavity blockage with sputum retention.

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PNEUMOPERITONEUM SUPPLEMENTING PHRENIC PARALYSIS[1,2]

ARNOLD B. RILANCE AND FREDERICK C. WARRING, JR.

Pneumoperitoneum has been used sporadically in the treatment of intestinal and peritoneal tuberculosis since shortly after the turn of the century. Some observers noted coincidental improvement in the associated pulmonary disease. In 1933 Vadja (1) first reported the use of pneumoperitoneum to elevate the diaphragm in patients with pulmonary tuberculosis. He described 2 cases, both of which had a normally functioning diaphragm. Since then, there have been numerous reports about the procedure in the European, South and North American literature. In the great majority of the cases recorded, pneumoperitoneum was used alone, without phrenic paralysis. Many of these cases were far advanced, with bilateral disease and a very poor prognosis, on which other collapse measures had been unsuccessful or were not feasible. It is to be expected that the results obtained in such cases would not be too satisfactory.

Our experience with pneumoperitoneum has been confined solely to its use to supplement phrenic paralysis. Indications in these cases were those usually accepted for phrenicectomy alone. It was found that frequently the combined procedure produced cavity closure and sputum reversal, where the phrenicectomy alone, after adequate trial, had failed.

Banyai (2), Joannides (3) and Fremmel (4), among others, have commented about the marked additional elevation of the hemidiaphragm that is frequently obtained after the induction of pneumoperitoneum in cases with phrenic paralysis. However, one fails to find any report of a consecutive series of such cases, from which one can formulate an opinion as to the results to be expected from such a method of treatment. The material in this paper represents the results obtained by the use of supplementary pneumoperitoneum in a consecutive series of 55 cases of pulmonary tuberculosis treated by phrenicectomy. The patients have been observed for a period of time varying from twelve to thirty-five months.

[1] From the Laurel Heights State Tuberculosis Sanatorium, Shelton, Connecticut.
[2] Read before a meeting of the Connecticut State Tuberculosis Physicians.

An appreciable number of cases observed for a shorter period of time have not been included, though the results have been comparable. In spite of the small number of cases, the period of observation appears adequate to permit drawing tentative conclusions as to the value of the procedure.

THEORY

It is generally believed, other factors being equal, that the beneficial results obtained from phrenic paralysis are in direct proportion to the degree of elevation of the paralyzed hemidiaphragm. That this varies tremendously from one patient to another is a well recognized fact. The force bringing about this elevation is that exerted by the pressure differential that exists between the abdominal and pleural cavities. If no other factors were involved, the complete loss of muscular tone that results from adequate paralysis of the phrenic nerve would allow a maximum elevation to take place in every case.

Certain factors, such as the normal variations in intrapleural pressure, the contraction of fibrous tissue in the diseased lung, consolidation of the lung, pleural effusions and thick adherent pleurae, have been recognized as influencing the elevation obtained after phrenic paralysis. Little attention, however, has been paid to possible intraäbdominal factors that may also influence the rise of the hemidiaphragm.

It appears obvious that, when the hemidiaphragm moves up into the thoracic cage following paralysis, it acts in such a way as to increase the size of the abdominal cavity. There are two possible ways in which this may be compensated. The abdominal viscera may adjust themselves to occupy the increased space created. Second, the anterior abdominal wall, which is the only nonrigid boundary of the abdominal cavity, through retraction and resultant reduction in the anteroposterior diameter, may compensate for the increase in the superoinferior diameter of the cavity. Failure of adequate readjustments of this nature would prevent or impair the elevation of the hemidiaphragm that would otherwise take place. In the majority of patients these readjustments appear to be such as to allow only a limited elevation of the diaphragm, rather than the maximum that is possible in the individual case. This is suggested by the fact that, in 67 per cent of the 55 cases reported here, appreciable to marked added elevation resulted from the induction of pneumoperitoneum.

The action of pneumoperitoneum in bringing about this marked added elevation cannot be explained on the basis of pressure changes. Maxi-

mum elevation was practically always obtained before any appreciable change in the intraäbdominal pressure was noted. Moreover the introduction of large quantities of air and attempts to maintain high intra-abdominal pressure did not result in any further material rise of the hemidiaphragm.

It is, therefore, most likely that the air introduced into the peritoneal cavity acts merely by occupying the extra space created by the rise of the hemidiaphragm. The presence of this air allows the elevation to become maximum.

It has been contended that this added elevation only lasts as long as the patient is in the upright position and the air remains under the diaphragm. This has not proved to be the case. If the patient is viewed under the fluoroscope and is tilted from the upright into the supine position, it is noted that the air is partly or completely displaced from the subphrenic space. The diaphragm however remains at the same level. This observation substantiates the hypothesis that the effect of pneumoperitoneum supplementing phrenic paralysis is not due to any pressure that is exerted by the air under the diaphragm, but rather due to its space filling properties. It should be pointed out that the effect of pneumoperitoneum in the individual with an intact diaphragm is, in this respect, probably entirely different.

TECHNIQUE

Details of the technique of inducing and maintaining pneumoperitoneum are described by other writers. We have found it convenient to give the first few injections of air with the patient in the supine position, inserting the needle at a point about one inch to the left of the outer border of the left rectus muscle and about two inches below the costal margin on that side. After the pneumoperitoneum pocket is well established, subsequent refills are made with the patient lying on the side opposite to the paralyzed hemidiaphragm. The needle is inserted in the midaxillary line in one of the lower interspaces, after determining the best level by fluoroscopy. At first, refills average 600 cc. twice a week. Later, 500 to 700 cc. weekly are usually enough to maintain the elevation of the hemidiaphragm. Following refills, pressures in the subphrenic space are usually slightly positive. After the diaphragm has reached its maximum elevation, as determined by fluoroscopy or serial roentgenograms, larger refills and high pressures serve only to produce distension and increase the accumulation of air under the unparalysed hemidiaphragm.

COMPLICATIONS

There are several complications that may arise in the course of a pneumoperitoneum. Subcutaneous emphysema results from faulty position of the induction needle and causes local pain and crepitus. Air accidentally placed in the retroperitoneal tissues may even spread along the leaves of the diaphragm to produce mild degrees of mediastinal or cervical emphysema.

Slight accumulation of fluid in the abdomen occurs occasionally. It has never been a problem and has never resulted in the formation of adhesions, and, with one exception, has not required aspiration. This one patient, upon coughing, would fill an already existing small inguinal hernia sac with serous fluid. The hernia could not be reduced until about 25 cc. of the fluid had been aspirated. Aggravation of existing hernial defects by increased abdominal pressure is to be guarded against.

Pneumothorax may be induced inadvertently by inserting the needle too high in the axillary line. If this occurs, the effectiveness of the pneumothorax should be evaluated and the decision then made whether to maintain or abandon the pneumothorax pocket.

Pain in the region of the diaphragm or radiating to the shoulder is frequently encountered during the first few days of a newly established pneumoperitoneum. It is relieved by analgesics and soon disappears. In an occasional case the discomfort of intraäbdominal air may necessitate abandoning pneumoperitoneum, but this is unusual.

The most serious complication is air embolism. This may either be induced at the time of a refill or may occur spontaneously. In one case a small amount of air was accidentally injected into the venous system at the time of a refill. The patient received supportive treatment and recovered uneventfully and without sequelae. One other patient (5) died from spontaneous air embolism, brought on by vomiting and occurring four days following the last refill. Although the incidence of air embolism has been unduly high, it is of interest that both instances occurred in patients treated early in the series. With increased experience and adequate care, no other instances of air embolism have been noted, and in all probability the actual incidence of air embolism in a larger series of cases will be appreciably smaller.

RESULTS

Pneumoperitoneum was induced following phrenic paralysis in a consecutive series of 55 cases in an attempt to increase the elevation of

the paralyzed hemidiaphragm. In most instances the effect of the phrenic paralysis alone was observed for a period of from one to two months, before beginning the pneumoperitoneum. Patients who had a phrenicectomy, and had shown marked improvement before pneumoperitoneum could be started, did not receive the treatment and were not included in this series. In no instance was pneumoperitoneum used with phrenicectomy to supplement an ineffective pneumothorax. The patients presented the usual indications for phrenicectomy. In certain instances arrest of the disease from phrenicectomy was not expected, but it was hoped that better control of the disease might allow a thoracoplasty to be performed at a later date.

In each case, measurements were made of the elevation of the hemidiaphragm after phrenicectomy and again after the pneumoperitoneum was well established. Where the added elevation was 2.0 cm. or less, the procedure was considered mechanically ineffective and pneumoperitoneum was abandoned. In 18, or 33 per cent, of the 55 cases, insufficient rise was obtained and pneumoperitoneum was discontinued. The remaining 37 patients furnish the material for evaluation of the therapeutic results.

Of the 37 patients, one had minimal, 9 had moderately advanced and 27 had far advanced pulmonary tuberculosis. One patient had a negative sputum while 36 had persistently positive sputum before treatment. Fifteen of the 36 positive-sputum cases became consistently negative. Three patients have continued to show an intermittently positive sputum and, of these, 2 show definite evidence of tracheobronchial tuberculosis. Eighteen of the 36 remained consistently positive during and after treatment. Thirty-four patients, all with positive sputum, showed definite cavities by stereo-roentgenograms prior to treatment.

In these 37 mechanically satisfactory cases, rise of the hemidiaphragm after phrenicectomy averaged 2.8 cm. The average additional elevation from pneumoperitoneum was 4.1 cm. and the average total rise was 6.9 cm. (figure 1). In 86 per cent of the patients the total elevation was 5.0 cm. or more. In 62 per cent it was 7.0 cm. or more.

Closure of cavities was gratifying. In the 34 cavity cases, closure of cavities was affected in 19 (56 per cent). In 2 cases the cavities were questionably closed, and in 10 more the cavities became smaller.

Cavities of various sizes seemed to respond almost equally well (table 1). There were 41 cavities seen in the 34 cavity cases; 23, or 56 per cent, of all cavities closed.

It probably would be expected that a higher incidence of cavity closure would be found in those cases where the cavity was located in the lower third of the lung field. This was found to be true (table 2). Apical cavities showed second best response, with cavities located in the middle third of the lung field manifesting the smallest percentage of closure.

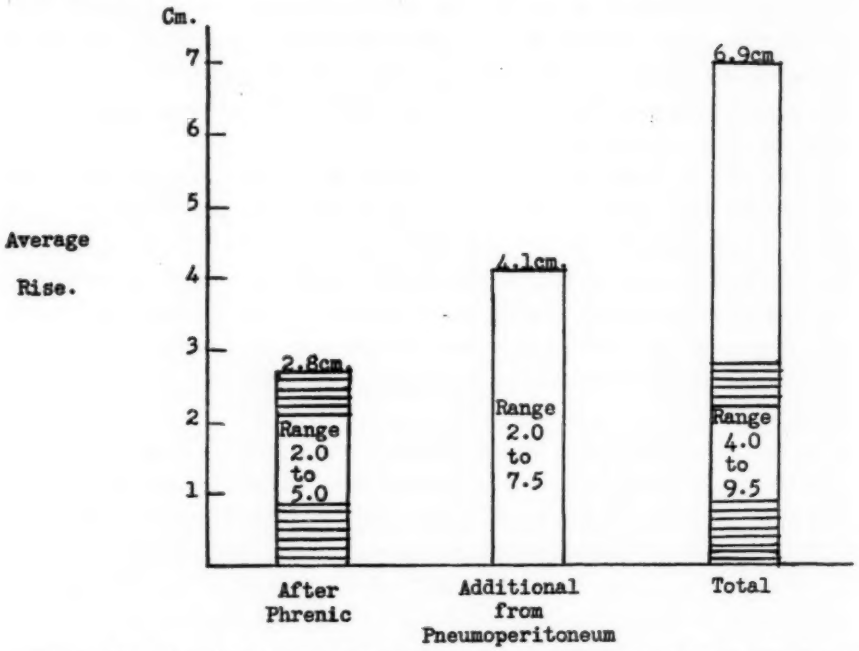

FIG. 1. Elevation of diaphragm in 37 cases. Eighteen of the original 55 patients did not receive an additional elevation of more than 2.0 cm. and are not included.

CASE HISTORIES

Case 1: G. C., white male, age thirty-three. Admitted for the first time on March 16, 1934 with moderately advanced tuberculosis, with cavitation in the right apex. A right temporary phrenic paralysis in October, 1935, was made permanent in February, 1937. He was discharged on October 30, 1937 in good general condition, but with an intermittently positive sputum. On readmission March 18, 1940, his roentgenogram (figure 2) showed a spread of disease in both lungs with a 5.0 cm. cavity opposite the seventh vertebral spine. He had physical signs suggestive of tuberculous bronchitis. Artificial pneumothorax was ineffective. On April 8, 1940 pneumoperitoneum was induced. Six weeks later his roentgenogram showed the cavity reduced to

1.0 cm. A roentgenogram taken July 17, 1940 (figure 3) shows the appearance of his lung with pneumoperitoneum well established, and the cavity closed. The added elevation of the right hemidiaphragm obtained by pneumoperitoneum measured 4.0 cm. The total elevation obtained measured 7.0 cm.

Case 2: J. C., white male, age twenty, admitted on November 2, 1938. He had been under treatment elsewhere for three months prior to admission. A review of his previous X-ray films demonstrated progressive clearing of a bilateral lesion. A small cavity in the right side was felt to be closed by

TABLE 1

Results of treatment by size of cavities

SIZE OF CAVITY	TOTAL	CLOSED	? CLOSED	SMALLER	UNCHANGED
2.0 cm. or less	9	6 (66%)	—	2 (22%)	1 (11%)
2.0 to 3.0 cm.	3	2 (66%)	—	1 (33%)	—
3.0 to 4.0 cm.	13	6 (46%)	1 (8%)	5 (38%)	1 (8%)
4.0 to 5.0 cm.	9	5 (56%)	1 (11%)	2 (22%)	1 (11%)
5.0 cm. or more	6	4 (66%)	—	2 (33%)	—
Multilocular	1	—	—	—	1 (100%)
	41* (100%)	23 (56%)	2 (5%)	12 (29%)	4 (10%)

* 41 cavities in 34 patients.

TABLE 2

Results of treatment by position of cavities

POSITION OF CAVITY	TOTAL	CLOSED	? CLOSED	SMALLER	UNCHANGED
Upper Third of Lung	25	14 (56%)	1 (4%)	8 (32%)	2 (8%)
Middle Third	10	4 (40%)	1 (10%)	3 (30%)	2 (20%)
Lower Third	6	5 (83%)	—	1 (17%)	—
	41* (100%)	23 (56%)	2 (5%)	12 (29%)	4 (10%)

* 41 cavities in 34 patients.

January, 1939. In April, 1939 he developed a reëxacerbation of disease and a 4.5 cm. cavity in the right lung reappeared. Artificial pneumothorax was unsuccessful. A right temporary phrenicectomy was performed May 8, 1939. Figure 4 demonstrates the lesion and elevation obtained after phrenicectomy. Pneumoperitoneum was started on May 12, 1939 and the cavity was felt to have become closed by October 12, 1939. His sputum became negative on concentration in August, 1939 and has remained so ever since except for two isolated positive specimens (Gaffky I). Figure 5 shows the X-ray appearance of the lesion with pneumoperitoneum well established and the cavity

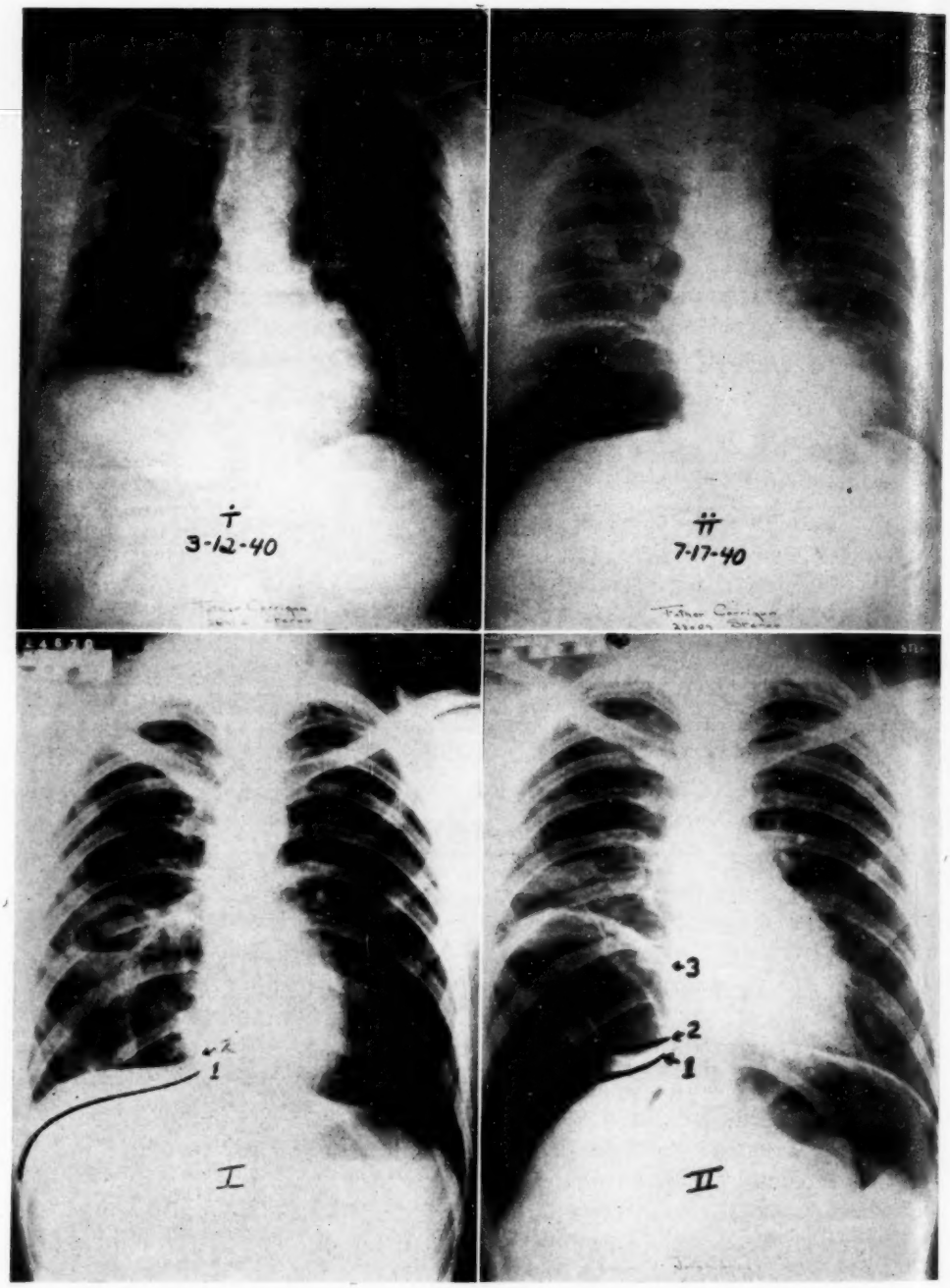

FIG. 2. Upper left. Right permanent phrenic paralysis performed in February, 1937 during previous admission.

FIG. 3. Upper right. Additional elevation from pneumoperitoneum measured 4.0 cm.

FIG. 4. Lower left. 1 represents the level of the diaphragm before paralysis; 2 the elevation obtained after phrenic paralysis, which measured 2.0 cm.

FIG. 5. Lower right. 3 represents the elevation of the diaphragm after pneumoperitoneum, which measured 6.0 cm.

closed. The measured rise of the right hemidiaphragm after phrenic paralysis was 2.0 cm. The added elevation obtained from pneumoperitoneum was 6.0 cm.

Case 3: A. S., white female, age twenty-two, was admitted March 21, 1938, following a pneumonic onset in May, 1937. She was under treatment elsewhere for nine months before admission, during which time she showed continued activity with development of multiple cavities in the right lung. Pneumothorax was attempted unsuccessfully. A right temporary phrenic paralysis was performed on May 5, 1938. A roentgenogram taken soon afterward (figure 6) shows the level of the right hemidiaphragm. Pneumoperitoneum was induced on May 27, 1938. By October, 1938 her temperature, previously reaching 100° F. daily, came down to normal. There was marked clinical improvement. Figure 7 shows the appearance of her roentgenogram with the maximum elevation of the hemidiaphragm. In May, 1939 it was decided to perform a thoracoplasty. After the pneumoperitoneum had absorped and the hemidiaphragm had descended to its former position, her disease became very active again. The operation was postponed and pneumoperitoneum was reinstituted. The activity again subsided and a thoracoplasty was performed over the pneumoperitoneum. In this patient, the marked additional elevation of the hemidiaphragm obtained through inducing pneumoperitoneum was felt to be the determining factor which brought about sufficient improvement to allow a thoracoplasty to be safely performed. The additional rise of the hemidiaphragm obtained from pneumoperitoneum measured 8.5 cm.

Case 4: J. R., single white male, age eighteen. Admitted May 22, 1940. The patient had an insidious onset in February, 1938 and a diagnosis of pulmonary tuberculosis was made in August, 1938. From September, 1938 till admission, a period of one year and eight months, he was under sanatorium treatment elsewhere. During this time his general health improved and extensive disease in the right lung cleared and organized, leaving no evidence of cavity. A cavity in the left apex, however, had gradually increased in size from 3 to 6.0 cm. in spite of adequate bed-rest. Artificial pneumothorax was tried unsuccessfully on the left side. A left temporary phrenicectomy was performed on June 17, 1940. A roentgenogram (figure 8) shows the rise after phrenic paralysis which measured 2.0 cm. Pneumoperitoneum was started on July 9, 1940. A roentgenogram of November 5, 1940 (figure 9) shows the maximum added elevation obtained from the pneumoperitoneum which measured 3.0 cm. The cavity has apparently closed and his sputum has just recently become negative on concentration of forty-eight hour specimens of sputum. Though the additional rise from pneumoperitoneum was not marked, the total elevation obtained is appreciable.

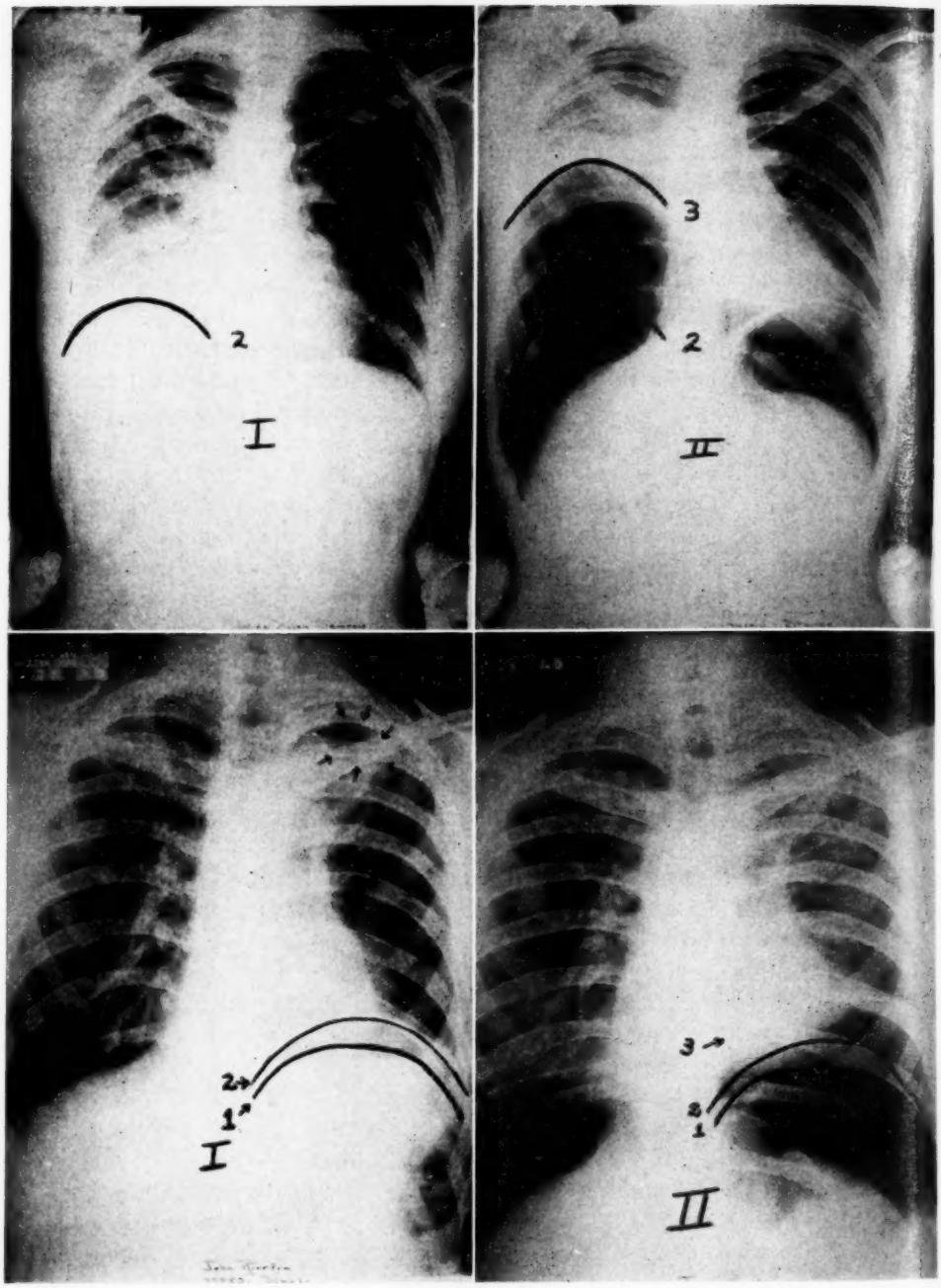

FIG. 6. Upper left. 2 represents the level of the diaphragm after paralysis.

FIG. 7. Upper right. 3 represents the elevation of the diaphragm after pneumoperitoneum, which measured 8.5 cm.

FIG. 8. Lower left. 1 represents the level before paralysis; 2 the elevation after phrenic paralysis, which measured 2.0 cm.

FIG. 9. Lower right. 3 represents the elevation of the diaphragm after pneumoperitoneum, which measured 3.0 cm.

COMMENT

Nehil and Alexander (6) report closure of cavity by phrenic paralysis alone in 38 per cent of 179 cases. Cavities became smaller in 16 per cent, were unchanged in 24 per cent and increased in size in 20 per cent. In a series of 378 cavity cases out of a total of 500 cases treated by phrenicectomy, O'Brien (7) reported cavity closure in 50.5 per cent. In over one-third of these 378 cases, however, phrenic paralysis was used to supplement pneumothorax. If the pneumothorax cases are excluded, 38 per cent of the remaining 233 cases showed closure of cavities. Of the cases reported in this paper, 56 per cent of the cavities were closed by phrenicectomy supplemented by pneumoperitoneum. The difference of 18 per cent is felt to be of probable significance, in spite of the large inherent error possible in the statistical evaluation of a small series of cases.

The fact that an unusual proportion of large cavities were closed by the procedure was rather surprising. Four of the 6 cavities, 5.0 cm. or larger, were closed and the other 2 became smaller. Five of 9 cavities measuring 4.0 to 5.0 cm. diameter were closed, one was questionably closed and 2 became smaller; 60 per cent of 15 cavities 4.0 cm. or larger in diameter were closed.

The entire benefits from the procedure were not shown by cavity closure alone. Seven patients, whose cavities were not closed by phrenicectomy and pneumoperitoneum, later had successful thoracoplasties. Of these, 2 cases had rapidly progressing tuberculosis even after phrenicectomy. Their disease was felt to be too active to warrant thoracoplasty at that time. Both had a marked additional rise of their hemidiaphragms after pneumoperitoneum with resultant rapid subsidence of fever and decrease in size of cavities with general clinical improvement. These 2 patients were definitely converted into good surgical risks by the addition of pneumoperitoneum.

CONCLUSIONS

Pneumoperitoneum is slightly more difficult technically to administer than pneumothorax. Nevertheless it is a safe procedure, causes no more discomfort or inconvenience than pneumothorax and can be maintained in ambulatory patients.

Though a statistical evaluation of a small series of cases, such as this one, is always open to question, actual experience with individual cases which have failed to respond to phrenic paralysis alone, but have obtained a satisfactory result by supplementing the phrenic paralysis with pneumoperitoneum, proves the procedure to be of merit.

In this series slightly more than 50 per cent of the patients had evidence by X-ray of closure of cavity, and slightly less than 50 per cent had sputum converted to negative or residual positive sputum could be explained by demonstrable bronchial ulcers.

It should be remembered that pneumoperitoneum acts only by its ability to make a phrenicectomy a more effective procedure, by bringing about added elevation of the hemidiaphragm. It has been found true that cases unsuitable for phrenic paralysis in the first place rarely have received much benefit from supplementary pneumoperitoneum. Pneumoperitoneum should be given a fair trial in those selected cases felt to be amenable to treatment by phrenicectomy, where adequate trial of phrenicectomy alone has proved to be inadequate.

SUMMARY

1. Fifty-five patients received pneumoperitoneum to supplement phrenicectomy.

2. In 18 (33 per cent) of the cases, pneumoperitoneum was abandoned because of insufficient additional rise of the diaphragm.

3. Elevation of the hemidiaphragm in mechanically effective cases averaged 2.8 cm. after phrenicectomy. Additional elevation following pneumoperitoneum averaged 4.1 cm. The average total elevation measured 6.9 cm.

4. Results of treatment are presented, showing the effect on sputum, and the number, size and position of the cavities.

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CONTROL OF TUBERCULOSIS IN AN INSTITUTION FOR THE MENTALLY ILL[1,2]

SAMUEL S. ALTSHULER AND LOUIS J. BAILEY

That every case of tuberculosis comes from another case is a fact too well known to need elaboration. It has also been shown in group survey studies that the highest incidence of tuberculosis is among those who give a history of contact with a tuberculosis patient. In view of these factors, precautions are advised for all persons coming in contact with a known case of tuberculosis so that the spread of the disease may be checked. However, there are those suffering from tuberculosis who are unaware of their illness and with whom consequently the proper precautions are not observed. These unrecognized cases are a great danger.

This danger is even greater in institutions for the care of the mentally ill than it is in the community at large. In such institutions inmates associate intimately with each other and their habits of hygiene are bad. Many inmates remain in these institutions for long periods of time and, if there is an unrecognized case of tuberculosis among them, they have every opportunity to contract the disease.

The danger is not alone to the inmates. An unrecognized case of tuberculosis may spread the infection to attendants, doctors, nurses and social workers. Friends and relatives who visit the patient are also exposed. Thus, the institution may become a focus for tuberculosis infection.

In 1934 tuberculosis was discovered in patients who had been in the wards for the mentally ill at Eloise Hospital for five years or more. In some cases X-ray films which had been taken on admission were negative for the disease. It was, therefore, rather suggestive that these patients might have become infected with tuberculosis after entering the institution. The extent of the disease became apparent in 1935 when there were 38 autopsies on patients dying in the mental hospital and, of these, 8, or more than 20 per cent, were found to have tuberculosis of the lungs.

[1] This is a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Public Health at the University of Michigan.

[2] From the Division of Psychiatry, Eloise Hospital, Dr. Martin Hoffman, Clinical Director, Eloise, Michigan, and Wayne University College of Medicine.

This, then, was the problem: First, to make a survey of the institution to find all persons with tuberculosis, and, second, to establish a program for the control of the disease in the institution.

Several studies on the extent and the nature of this situation have been reported.

Burns (1) investigated the incidence of tuberculosis in Minnesota state institutions. Among others, these included hospitals for the mentally ill and schools for feeble-minded patients and epileptics. He did tuberculin tests on 15,994 inmates and 2,400 employees; the positive reactors were X-rayed and sputum and stool studies were made. Of the inmates, 82 per cent showed reactions to the tuberculin test, and of the employees, 72 per cent were reactors. Of those X-rayed, 9.2 per cent of the inmates and 3.7 per cent of the employees had tuberculosis. About 12 per cent of the total deaths in these institutions were due to tuberculosis. Of these, 33 per cent occurred one year or less after admission. Presumably, these persons came into the institution with the disease. Fifty-one per cent of the tuberculosis deaths were those of inmates committed five years or more. Most likely this group developed the disease as a result of contact with cases in the institution. Burns concluded that all persons entering these institutions should be tuberculin tested and the reactors should be X-rayed; that all inmates should be X-rayed periodically; that all employees should be tuberculin tested upon hiring and that the reactors should be X-rayed; and finally, that cases of tuberculosis with positive sputum should be segregated.

Bogen, Tretz and Grace (2) studied inmates of the Longview State Hospital at Cincinnati, where a tuberculosis mortality rate of 7 per 1,000 was discovered. This was ten times that of the general population in that state.

Fishberg (3) says that tuberculosis is the cause of over 50 per cent of the deaths in institutions for the care of the feeble-minded and 30 per cent in institutions for the insane. Plunkett (4) says that the tuberculosis death rate averaged 812 per 100,000 in the New York state hospitals for the mentally ill. McGlure and Brink (5) found that the percentage of deaths due to tuberculosis was twice as high in mental hospitals as in the whole population. They did tuberculin tests and X-rays on an inmate population of 10,500 and on members of the staff and found tuberculosis in about 7 per cent of the former and about 2 per cent of the latter.

CASE-FINDING IN THE INSTITUTION

Eloise Hospital is a county institution to which insane patients are committed through the Probate Court. The hospital has an inmate population of about 3,600, with an admission rate of 100 to 150 a month. There are about 1,200 employees. Most of the patients are able to be up and around; they are housed in large wards, which means that they are in very close association. A few violent ones are confined in single rooms and a few are bed patients.

During the time of this study, the total inmate population was 4,708. Of these, 4,477 had some kind of examination for tuberculosis; the remaining 231 died or were paroled before they could be examined.

In making the survey at Eloise, the following methods were used successively:

1: Tuberculin testing of inmates and employees with X-ray examination of reactors.
2: Routine X-ray examination of all inmates.
3: Fluoroscopic examination of inmates and employees with X-ray examination of those who showed suspicious fluoroscopic findings.

No attempt was made to try other techniques which have been suggested—the micro film (6) or the sensitized paper film (7)— because these would have involved expenditure for special equipment.

In all of the procedures used, the final diagnosis was made from X-ray findings which were classified in the following manner:

1. Negative
2. Nontuberculous
   - A. Pneumonoconiosis without tuberculosis
   - B. Pneumonitis
     - Lobar pneumonia
     - Bronchopneumonia
     - Diffuse pneumonitis
   - C. Bronchiectasis
   - D. Abscess
   - E. Tumor
3. Insignificant findings
   - A. Healed parenchymal nodules
   - B. Healed bronchopulmonary and tracheobronchial lymph nodes
   - C. Pleural thickening

4. Significant findings
   A. Active tuberculosis
      Tuberculosis with cavity
      Tuberculosis without cavity
      Effusion
   B. Other significant findings
      Tuberculosis scars
      Tuberculosis suspect

The classifications "Tuberculosis scars" and "Tuberculosis suspect" were included among the significant findings because, in making recheck examinations of the patients who had been so classified on first examination, a large part of the group were found to have active tuberculosis.

At the outset of the study, tuberculin testing was applied to 2,857 inmates and to 354 employees. The Mantoux test with Old Tuberculin was used in ascending doses starting with 0.01 mg. and repeating the test on negative cases with 0.1 mg. and then 1.0 mg. The following results were obtained:

	Number tested	*Positive*
Admitting wards	447	220 (49%)
Hospital wards	2,410	2,137 (88%)
Employees	354	283 (80%)

The comparatively small incidence of reactors in the admitting wards suggests that patients who are admitted without infection may acquire it in the institution.

Of the reactors among the inmates, 778 were X-rayed with these results:

Negative	132
Nontuberculous and insignificant	479
Active tuberculosis	27
Other significant findings	140
Total	778

Only 27, or 3.5 per cent, of these persons were found to have active tuberculosis. Since only about 18 per cent of the subjects included in the survey were eliminated from X-ray by the tuberculin testing, and since the number of active cases found was so small, it was decided that the amount of screening accomplished by the tuberculin test was not sufficient to warrant the time and effort involved.

The second method of case-finding attempted was routine X-raying of

all new admissions and of all patients not previously X-rayed. These latter were taken in alphabetical order. This procedure was carried out on 1,268 persons with the following results:

Findings	*New Admissions*	*Inmates*	*Total*
Negative	375	213	588
Nontuberculous and insignificant	295	144	439
Active tuberculosis	21	18	39
Other significant findings	118	84	202
Total	809	459	1,268

Among the new admissions 21, or 2.6 per cent, were found to have active tuberculosis; among the inmate group the incidence was 3.9 per cent. The routine X-ray program had to be abandoned because the volume of work required far exceeded the capacity of the X-ray department. With the large admission rate it became plain that the task could never be completed.

The fluoroscopic examination was then begun as a screening method and it was found to be so satisfactory that the survey was completed on this basis. The plan was to make a fluoroscopic examination of all inmates and members of the staff who had not as yet been examined in the survey. Those with suspicious fluoroscopic findings were X-rayed. In this group 1,601 inmates and 669 employees were examined. Of the inmates 210, or 12.6 per cent, were fluoroscopically positive; among the employees 75, or 11.2 per cent, were fluoroscopically positive. These suspicious cases were X-rayed with the following results for the inmate group:

Negative	40
Nontuberculous and insignificant	28
Active tuberculosis	30
Other significant findings	112
Total	210

The 30 cases of active tuberculosis represent 14.3 per cent of the inmates X-rayed in this portion of the survey. This is a very high yield, and is the best indication of the efficiency of the fluoroscopic examination as a screen. However, these 30 cases give an incidence of 1.87 per cent active tuberculosis in the entire group of 1,601 persons so examined. Since this is so much lower than the 3.9 per cent found by routine X-ray of the inmates and the 2.6 per cent found by routine X-ray of the new admissions, it must be suspected that some cases were overlooked by this

method. Nevertheless, it is felt that the cases which were missed must have been minimal, and that this might be a significant loss in a one-time survey but that in an annual examination—such as this is to be—these cases would not long be ignored.

As a supplementary procedure, a recheck X-ray examination was made on those subjects whose first X-ray examination showed lesions which could not be classified definitely as active, and also on those subjects whose first X-ray examination came under one of the headings included in "Other significant findings." The second examination was made one to six months after the first. On 189 patients so reëxamined, the findings were:

Negative	8
Nontuberculous and insignificant	29
Active tuberculosis	23
Other significant findings	129
Total	189

The 23 cases of active tuberculosis which were found by this method give an incidence of 12.2 per cent for the group, which confirms the necessity for reëxamination.

Results of these various case-finding methods are summarized in table 1.

Altogether 276 cases of active tuberculosis were discovered among the inmate population. In addition to the cases found by the survey, a certain number had been diagnosed before the survey began, and others were found by X-ray examinations ordered because of signs or symptoms before the patient concerned had been reached by any of the survey methods.

The discovery of cases of tuberculosis in relation to the length of time these patients had been in the institution was as follows:

Under one year	5
One through four years	90
Five through nine years	89
Ten years and over	92
Total	276

It is seen that one-third of the total number of patients found to have tuberculosis had been in the institution for at least ten years. Two-thirds had been in the institution five years or longer. Only 5, or 1.8 per cent, were discovered during their first year.

The age composition of the group found to have tuberculosis was as follows:

Under 20 years	1
21 to 40 years	107
41 to 60 years	123
61 to 80 years	33
81 years and over	3
Total	276

In analyzing the 276 cases by psychiatric diagnosis, 144, or 52.1 per cent, are discovered to have dementia praecox. However, when a

TABLE 1

X-ray findings among inmates according to the method of group examination

METHOD OF GROUP EXAMINATION	NEGATIVE	SIGNIFICANT					INSIGNIFICANT					TOTAL
		Active Tuberculosis			Scars	Tuberculosis suspect	Pneumonoconiosis	Pneumonitis	Bronchiectasis	Tumor	Others	
		With cavity	Without cavity	Effusion								
Tuberculin test	132	21	6		131	9	6	1			472	778
X-ray survey inmates	213	13	5		77	7	2				142	459
X-ray new admissions	375	10	10	1	115	3	1	1	2	1	290	809
Fluoroscope	40	10	19	1	92	20	2	1			25	210
Total	760	54	40	2	415	39	11	3	2	1	929	2,256

distribution of the entire inmate population is made (table 2), this concentration is found to be not significant. It is therefore concluded that the type of mental disorder is not related to susceptibility to tuberculosis, except insofar as it affects the length of time in the institution.

Because of a variety of departmental policies and regulations, study of the employees could not be carried out in the same way as that of the inmates. While departmental requirements vary considerably, it is expected that in the future every employee will have a roentgenological examination at the time of hiring.

Of the 669 employees who were fluoroscoped, 75 had suspicious findings. Upon X-ray of 70 (5 have not yet been examined) 5 were found to have

significant lesions. Together with these 5, X-ray films taken for other reasons showed active tuberculosis as follows:

Attendants	34*
Nurses	4**
Occupational therapists	3
Stenographers	1
Total	42

* 2 on tuberculosis wards.
** 1 on tuberculosis wards.

TABLE 2

Distribution of inmate population by psychiatric diagnosis compared to similar distribution of patients with tuberculosis found in survey

PSYCHIATRIC DIAGNOSIS	INMATE POPULATION		TUBERCULOSIS PATIENTS	
	Number	Per cent of all inmates	Number	Per cent of all tuberculosis cases
Psychosis with syphilis	409	11.8	37	13.4
Alcoholic psychosis	109	3.2	7	2.5
Psychosis with cerebral arteriosclerosis	160	4.7	8	2.9
Senile psychosis	158	4.6	11	4.0
Manic-depressive psychosis	380	11.0	25	9.1
Dementia praecox (schizophrenia)	1,501	43.8	144	52.1
Paranoia	133	3.9	6	2.2
Mental defectives	88	2.6	7	2.5
Without psychosis	203	5.9	1	0.4
All others	291	8.5	30	10.9
Total	3,432	100.0	276	100.0

COST OF SURVEY

The cost of X-raying in this large group would have been from $1.20 to $1.50 per person. To examine 5,000 people by this method would cost from $6,000 to $7,500. Fluoroscopic examination costs about seven cents per person, so that the group can be examined by this method for $350. Adding the cost of X-raying approximately 15 per cent of persons who may be expected to show suspicious fluoroscopic findings, the total cost of surveying the institution by this means is about $1,600. This estimated cost includes professional time, and assumes the purchase of no additional equipment since the fluoroscope was already in use in the institution.

SEGREGATION OF TUBERCULOSIS PATIENTS

Cases of tuberculosis found among inmates are classified according to the criteria of the National Tuberculosis Association as minimal, moderately advanced, and far advanced. For administrative purposes, the patients are also classified as active or inactive, and the active group is further divided into sputum-positive and sputum-negative cases.

Two types of tuberculosis wards have been established in the institution: one for the active cases and one for the convalescent patients who have been transferred from the active wards. The convalescent ward is for the purpose of observing the quiescent cases until such time as it is felt that there will be no reactivation and that the tuberculosis is arrested. When the patient has arrived at this latter stage, he is ready to be transferred to the open ward and to mingle with nontuberculous patients. The convalescent wards also house patients who are receiving pneumothorax treatments.

At the present time, the tuberculosis patients are kept on three wards of one of the buildings assigned to the mentally ill patients. Two wards house the male patients and the other the female patients. When and if the number of patients with tuberculosis is sufficient to occupy the entire building, the nontuberculous patients will be transferred elsewhere.

The technique of caring for these patients is essentially the same as that followed in a tuberculosis sanatorium, but it is not commonly used in hospitals for the mentally ill nor in general hospitals. Specifically, the recommendations of Oatway (8) have been followed as far as possible.

When a patient is found to have active tuberculosis, it is then determined whether his sputum is positive or negative and he is placed in the active ward accordingly. The positive-sputum cases are segregated, or placed in separate rows, or toward the end of a row, depending upon the number of positive cases in the ward. A ward map is kept in the nurses' office and red and green thumb tacks are used to indicate whether the patient has a positive (red) or a negative (green) sputum. Sputum studies are made once a month and the results are indicated on this ward map. The date of the sputum examination is indicated on the head of the thumb tack in white water-soluble ink. After a patient has six months of negative sputum, he is removed to the sputum-negative part of the ward. If a patient who has been negative becomes sputum-positive, three more daily examinations are made, and if they are consistently positive the patient is transferred to the sputum-positive section.

In sanatoria and other institutions for the care of tuberculosis patients, the patient is able to coöperate in the observation of the necessary precautions. Yet even in these institutions there is danger to the attendants. It has been found (9) that nurses engaged in caring for tuberculosis patients show evidence of having become infected. In a hospital for the care of mentally ill patients the problem is even more acute. No confidence can be placed in the ability of these patients to observe the strict isolation techniques which are desirable. Some of them are hostile, spitting at the nurses and attendants. Because of this a grave responsibility falls upon the attendants who for their own safety must learn to observe the strictest precautions. Special lectures are given to the attendants from the tuberculosis wards to impress upon them the importance of following the techniques recommended.

The treatment of tuberculosis in mentally ill patients is exactly the same as that given other tuberculosis patients. The forms of treatment used are bed rest, pneumothorax, supplemented with pneumonolysis if indicated, phrenicectomy or phrenicotomy, thoracoplasty and pneumoperitoneum.

Little difficulty has been encountered in giving pneumothorax treatments to any of these patients. One hundred have been given pneumothorax and in only one case were the treatments discontinued because of the patient's refusal to coöperate.

SUMMARY

Among the 4,477 inmates handled in this survey, 276 cases of tuberculosis have been found, giving a rate of 62 per 1,000. Among 1,200 employees, 42 have been found to have tuberculosis, giving a rate of 35 per 1,000.

The control of tuberculosis in an institution such as Eloise will be effected only when the majority of cases are discovered in the minimal stage, at which time they are curable and noncontagious, and when the active cases are segregated so that they will not serve as a focus of infection for the other patients.

A program for the control of the disease must, therefore, provide for the following measures:

1: Detection of tuberculosis lesions by

a. Examination of every patient at time of admission.

b. Periodic reëxamination of the inmate population and the staff so that newly developed lesions may be found in an early stage.

2: Segregation of the patients known to have tuberculosis and observation of strict isolation precautions.
3: Treatment of tuberculosis.

In order to discover the lesions as early as possible, the ideal arrangement would be to have periodic routine X-ray examinations of all inmates and all attendants. However, this would be a very expensive procedure; indeed, in so large an institution as Eloise the cost is prohibitive. In view of this practical consideration, the following plan, based upon experience obtained in making this survey, is offered:

1: All newly admitted patients and all employees at the time of employment should have a physical and fluoroscopic examination. Those showing suspicious findings by fluoroscopic examination should have an X-ray film.
2: Every patient and member of the staff should have an annual fluoroscopic examination to be followed by an X-ray film in the event that suspicious findings appear.
3: Any person upon whom the X-ray findings are questionable should be reexamined in from six weeks to six months.

The authors wish to acknowledge with thanks the assistance of Dr. Morris Raskin, who did the necessary tuberculin testing.

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TUBERCULOSIS IN MEDICAL STUDENTS[1]

HOWARD L. ALT, EARL E. BARTH AND ALEXANDER A. DAY

In late years considerable attention has been given to the subject of tuberculosis in medical students. This attention is warranted because of the age susceptibility of the group along with the increased hazard of exposure to infection. Soper and Amberson (1) recently have reviewed the occurrence of tuberculosis in various medical schools in this country. In some schools the incidence was alarmingly high, but in the majority of instances it did not appear to be excessive. Interest in this subject has been especially stimulated by the thorough studies of Hetherington and his associates (2) at the University of Pennsylvania Medical School. In their report of 1935, they found that, among 400 students, clinical tuberculosis developed in 2 per cent during the medical course and an additional 3 per cent developed advanced latent infiltrations that were a serious menace to health.

The purpose of the present report is to summarize our own experiences with tuberculosis among students at the Northwestern University Medical School. We employed no case-finding program outside of routine physical examinations until 1933. Since the school year 1933–1934, single roentgenograms of the chest have been made on all freshmen and since 1935–1936, on all seniors at the end of the fourth year. Additional films were always made on individual students when the slightest indication arose. Tuberculin tests were performed on all students during 1935–1936. Since that time, all freshmen have had tuberculin tests and negative reactors have been retested each year. Students becoming positive to tuberculin have had roentgenograms of the chest at that time. Most of the subjects covered by this survey were in the age group between twenty-one and twenty-six years. The majority were men as there were only 4 women in each class. Before entering medical school, our students for the most part had lived in small cities and towns in the middle and far west.

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RESULTS OF TUBERCULIN TESTS

Tuberculin tests were done by the Mantoux method with the two official doses of Purified Protein Derivative[2] and readings made in forty-eight hours. The results are summarized in table 1. Tuberculin tests on first, second and third year students were performed during the first half of the school year, while those on fourth-year students were done shortly before graduation. After the initial positive tuberculin reaction on a student, the test was not repeated but continued in the table in subsequent years as positive. It is possible that some of these may have become negative later in the medical course. Students who were tested for the first time in years later than the initial testing of their class are not included in the table.

TABLE 1

Percentage of tuberculin reactions in medical students

CLASS	FIRST YEAR	SECOND YEAR	THIRD YEAR	FOURTH YEAR
1936				89.0
1937			97.0	99.0
1938		68.1	89.4	91.5
1939	66.1	84.4	89.0	89.9
1940	87.7	89.5	96.5	97.4
1941	64.9	72.6	77.8	
1942	68.7	77.1		
1943	43.7			
Average.....	66.2	78.3	89.9	93.4

In five first-year classes, 66.2 per cent of the students had positive tuberculin reactions. There is no apparent reason for the relatively low percentage (43.7 per cent) in the first-year class of 1943 as compared with other first-year classes. Negative reactors in this class were tested twice with second strength PPD in order to rule out any error in the procedure. In fourth-year classes reactors to tuberculin had increased to 93.4 per cent. This high rate of tuberculous infection in medical students is in agreement with the findings of others.

RESULTS OF ROENTGENOLOGICAL EXAMINATIONS

The results of all roentgenograms of the chest on medical students since the case-finding program was instituted are summarized in table 2. Tuberculous pulmonary lesions are arranged in four groups: namely,

[2] PPD Parke Davis and Company.

TABLE 2

Results of roentgenological examinations on medical students

YEAR	NUMBER OF ROENTGENOGRAMS TAKEN	CALCAREOUS DEPOSITS IN LUNGS OR TRACHEOBRONCHIAL LYMPH NODES	SUPRACLAVICULAR INFILTRATIONS	NONAPICAL INFILTRATIONS	COMBINED SUPRACLAVICULAR AND INFRACLAVICULAR INFILTRATIONS
Class of 1936					
32–33	12	3	0	0	1C
33–34	5	0	0	0	0
34–35	9	0	1	0	0 (1)
35–36	121	13	0 (1)	0 (1)	0 (1C)
Class of 1937					
33–34	103	15	4	1	1C
34–35	10	1	0	0	0
35–36	30	1	0	1	1
36–37	148	4	2 (1)	1C (1)	1
Class of 1938					
34–35	101	15	0	0	0
35–36	6	0	0	0	0
36–37	27	4	0 (1)	0	1C
37–38	132	1	0	1C	0
Class of 1939					
35–36	118	17	2	0	1C
36–37	18	0	(1) 0	0	0
37–38	31	3	0 (1)	1C	0
38–39	142	4	0	1	0
Class of 1940					
36–37	133	29	0	0	1, 1C
37–38	8	0	0	0	0
38–39	42	6	0	1 (1)	0
39–40	117	1	0	0	0
Class of 1941					
37–38	127	19	2	0	0
38–39	25	0	0	0	0
39–40	51	3	0	0	1C
Class of 1942					
38–39	124	18	1	0	0
39–40	23	0	0	0	0
Class of 1943					
39–40	129	15	0	0	0

Explanation of Table: Figures in parenthesis to right of main columns indicate initial roentgenograms during the medical course.

Under pulmonary infiltrations, figures in main columns occurring after first year in each class indicate that lesions were not present on initial roentgenograms.

Figure in parenthesis to left of main column under supraclavicular infiltrations, class of 1939, indicates progression of preexisting lesion.

Letter C denotes clinical tuberculosis, that is, symptoms or signs of the disease.

calcareous deposits in the lungs or tracheobronchial lymph nodes,[3] supraclavicular apical infiltrations, nonapical infiltrations, and combined supraclavicular and infraclavicular infiltrations. Since at times there may be a question about the presence of calcareous deposits in the lung or lymph nodes, films were reviewed by Dr. James T. Case[4] in addition to one of us (E. B.). It was his opinion that unequivocal calcifications were present in the films so listed in the table. Supraclavicular infiltrations include both softer shadows and older lesions such as linear strands and irregularities of the apical cap. The latter lesions showed no change on subsequent examinations. Among nonapical infiltrations are coin-like shadows, fan-shaped infiltrations and cavitations. Students with both pulmonary infiltrations and calcareous deposits are included under each heading in the table. Pulmonary infiltrations and calcareous deposits are recorded only in the year in which they were first detected.

As the great majority of roentgenograms were made in first- and fourth-year classes, only these will be analyzed for the general incidence of tuberculous lesions. Of 815 freshman students examined, 128, or 15.7 per cent, had calcareous deposits in the lungs or tracheobronchial lymph nodes and 14, or 1.7 per cent, had infiltrations in the upper part of the lung. In determining the total incidence of pulmonary lesions in the senior classes, all lesions first detected during the first three years of school and later seen in the fourth-year films are included. Of 660 students in the graduating classes who had roentgenograms of the chest, 31, or 4.7 per cent, had lesions at or near the apex. This incidence is very much lower than that reported by Hetherington and coworkers (2) who found an average of about 18 per cent of medical students in graduating classes to have lesions at or near the apex of the lungs. Details concerning students who developed tuberculosis during the medical course will be given later.

CORRELATION OF TUBERCULIN TESTS WITH ROENTGENOLOGICAL FINDINGS

Among 94 freshman students who had calcareous deposits in the lungs or tracheobronchial lymph nodes, 27 had a negative tuberculin test and 4 had a doubtful reaction. It thus appears that many of the students who had a primary tuberculous infection earlier in life had lost their sensitivity to tuberculin. A similar degree of anergy in young adults with pulmonary calcifications has been observed by others (3, 4).

[3] It is assumed that all calcareous deposits resulted from previous tuberculous infection. However, we know that other lesions, such as foreign body reaction, fungus, old empyema and haemorrhage, may at times produce calcifications in the chest.

[4] Professor of Radiology, Northwestern University Medical School.

Twelve students who developed pulmonary tuberculous infiltrations had tuberculin tests earlier in the medical course. In 4 of these, the reactions were negative. It is of interest that in this group the extent of the lesions and the morbidity were greater on the whole than in the 8 individuals who had positive tuberculin reactions. All of the previously negative reactors developed clinically manifest tuberculosis, whereas only 2 of the 8 with positive reactions had symptoms or signs of the disease. Malmros and Hedvall (5) have recently stressed the high morbidity and extensive character of tuberculous lesions that may develop in young adults with negative tuberculin tests.

THE DEVELOPMENT OF TUBERCULOSIS DURING THE MEDICAL COURSE

The development of pulmonary lesions among students in five classes during the four-year medical course is summarized in table 3. Of the

TABLE 3

Students developing pulmonary tuberculosis during medical course

CLASS	SECOND YEAR		THIRD YEAR		FOURTH YEAR		TOTAL	PER CENT	FIFTH YEAR	TOTAL 5 YEARS	TOTAL PER CENT
	Clin.	Lat.	Clin.	Lat.	Clin.	Lat.					
36	0	0	1	1	1	1	4	2.9	1	5	3.6
37	1	0	0	2	1	5	9	6.4	2	11	7.9
38	0	0	1	0	1	0	2	1.4	0	2	1.4
39	0	0	1	0	0	1	2	1.4	1	3	2.1
40	0	0	0	2	0	0	2	1.4			
Total	1	0	3	5	3	7	Av.	2.7			
	1		8		10						

Clin., clinical; lat., latent.

19 students listed, 13 had negative roentgenograms on admission to the medical school. The remaining 6 were found to have infiltrations on initial films in the junior or senior years. Because of the nature of these lesions, they are thought to have developed during the medical course and are considered as such in the following discussion. We recognize the possibility that in some of these students lesions could have been present on admission to the medical school.

Cases are listed as clinical when such symptoms as fever, cough, pleuritic pain, haemoptysis or râles were present, while latent cases were entirely asymptomatic. As the enrollment of each class averages 140 students, approximately 700 passed through the medical school between the years 1936 and 1940. During this time clinical tuberculosis de-

veloped in 7 students, or 1 per cent, and an additional 12, or 1.7 per cent, of the students developed latent infiltrations in the upper half of the lung. Thus, 2.7 per cent of the students who entered medical school during the years studied developed pulmonary lesions by the end of their fourth year.

Of the 19 cases, one was detected in the second year, 8 in the third year and 10 in the fourth year. The high incidence of tuberculosis during the last two years of school coincides with the exposure of students to patients with active pulmonary disease.

None of these students had sputum containing tubercle bacilli. Routine studies of the gastric washings for tubercle bacilli were not made.

Because of the relatively mild nature of the tuberculosis, 15 of the 19 students were allowed to remain in school after the pulmonary lesions were discovered. They were advised to modify their activity as much as possible and were kept under close supervision. In this group, 2 had definite progression of their lesions and subsequently spent a period of time in sanitoria. Two others had progression early in their internships and were forced to withdraw for a time. A fifth student, who had had haemoptysis and pleurisy with effusion during the summer between his first and second years, developed an apical infiltration during his interneship. The remaining 10 students have all improved without losing time from their regular program.

Progression of tuberculosis in the 2 students while in the medical school might have been prevented had they been required to drop out of school when the lesions were discovered. In the case of the 3 students who had progression during their internships, there was no reason for advising more conservative treatment while in school. In 2 of these, the lesions seen in the routine films at graduation were so slight that their real significance was only apparent when compared with the films after further development in the fifth year. The third student, who had had pleurisy with effusion, had no pulmonary infiltration while in school.

Improvement has ultimately occurred in all 19 students and none have been forced to give up their medical careers because of their disease. At the present time they are all leading active lives as students, internes or practicing physicians.

POSSIBLE FACTORS CONCERNED IN THE AETIOLOGY OF TUBERCULOSIS IN STUDENTS

Factors of possible importance in the development of tuberculosis in the 19 students in this series were previous history of tuberculosis,

family history, overwork and exposure to patients or classmates with tuberculosis.

One student had had pleurisy with effusion at the age of ten years. On admission to the medical school, his chest film was negative except for diaphragmatic pleural adhesions. He was found to have apical tuberculosis at the beginning of his third year.

Six of the 19 students had a family history of the disease. In 2 of these the relative involved did not have tuberculosis of the lungs and in a third there had been no contact with the case in the family. In only one instance was there recent contact with an active case in the family. This was a female student who was caring for a sister who died of tuberculosis while she (the student) was attending medical school. This student was found to have a supraclavicular lesion during her junior year. She had a pulmonary haemorrhage shortly after finishing school.

The heavy schedule of the medical course along with extracurricular work has frequently received part of the blame for the high incidence of tuberculosis in medical students. Thirteen (68 per cent) of the 19 students had positions outside of school just prior to the time that their lesions were detected. A recent survey has revealed that approximately 40 per cent of all of our juniors and seniors do some outside work. From these comparative figures, it seems possible that overwork might have played a rôle in the cause of tuberculosis in these students.

A factor of possibly greater importance is exposure to patients with active tuberculosis. In our series, as in others reported, the incidence of the disease was highest during the clinical years. One student had had a class at a tuberculosis hospital for three months while another had performed autopsies on several cases of tuberculosis. Four students remembered specifically having examined patients with active pulmonary lesions a short time prior to developing the disease themselves. Two others had worked as orderlies in general hospitals.

The possibility of tuberculosis having been spread by contact of students with each other is suggested by the high incidence of the disease in the class of 1937 (see table 3). The incidence during the four years in the class of 1937 was 6.4 per cent as compared to an average of 1.8 per cent in the other four classes studied. It may also be seen in table 1 that the increase in reactions to tuberculin was excessive in the entire student body during the year 1936–1937. In order to determine whether this increased incidence of tuberculosis in the class of 1937 continued into the fifth year, questionnaires were sent to four of the classes who had

completed one year of interneship. Replies were received from about 75 per cent of the members of each class who for the most part complied with the request to have a chest roentgenogram at that time. Pulmonary lesions had developed in one student in the class of 1936, 2 in the class of 1937, none in the class of 1938 and one in the class of 1939. This gives a total incidence in the four classes respectively for a five-year period of 3.6, 7.9, 1.4 and 2.1 per cent. The incidence of tuberculosis in the fifth year in the class of 1937 was comparatively low but was greater than in the other classes.

No obvious source of infection was present among students in the class of 1937. As previously stated, none of those affected had tubercle bacilli in the sputum. Of the 9 students who developed lesions in this class, 3 belonged to the same fraternity but none of them lived at their fraternity house. One of the students from this class who developed a pulmonary lesion in the fifth year was also a member of this fraternity. No other members of this fraternity were represented among the remaining 10 cases from other classes. No examinations were made on the rapidly changing personnel in the fraternity house in question. None of the employees at least had chronic coughs or other outward evidence of tuberculosis.

It should be noted that 2 students from the class of 1937 had pulmonary lesions at the time of admission to the medical school. Neither of these belonged to the fraternity mentioned above. Frequent films of the lungs showed regression of the lesions in both cases. A search of their gastric contents for tubercle bacilli was unfortunately not carried out. One of these students roomed for a year with a classmate who subsequently developed an apical infiltration. It is possible that one or both of these students were a source of tuberculous infection in the class of 1937. No other evidence of possible cross-infection between students was apparent.

An unusually high incidence of tuberculosis in single classes in medical schools has been observed by others. Hetherington and his colleagues (2) reported an incidence of 11.5 per cent pulmonary lesions in fourth-year medical students in the class of 1930 at the University of Pennsylvania. Nearly 10 per cent of the class of 1924 at Harvard Medical School became ill of tuberculosis during the course in the medical school or during their subsequent hospital work (6). It seems that the chances for cross-infection in medical schools would be great because of the close association of a large number of students over a long period of time.

From these observations, it appears possible that exposure to tuberculous patients and cross-infection among students were factors in the cause of tuberculosis in the group described. Overwork might also have been a contributing factor.

TABLE 4

Percentage of tuberculin reactions in dental students

CLASS	FIRST YEAR	SECOND YEAR	THIRD YEAR	FOURTH YEAR
39				68.6
40			67.9	69.6
41		58.5	77.4	
42	59.7	69.4		
43	54.3			

*Results of roentgenological examinations on dental students**

YEAR	NUMBER OF ROENTGENOGRAMS TAKEN	CALCAREOUS DEPOSITS IN LUNGS OF TRACHEOBRONCHIAL LYMPH NODES	SUPRACLAVICULAR INFILTRATIONS	NONAPICAL INFILTRATIONS	COMBINED SUPRACLAVICULAR AND INFRACLAVICULAR INFILTRATIONS
Class of 1939					
38–39	86	4	0	1C	1, 1C
Class of 1940					
38–39	2	1	0	0	0
39–40	47	3	0	0	0
Class of 1941					
37–38	62	12	1	2	1
38–39	5	0	0	0	0
39–40	13	0	0	1C	0
Class of 1942					
38–39	73	7	0	0	0
39–40	2	0	0	0	0
Class of 1943					
39–40	70	8	0	0	0

* For explanation of table, see table 2.

COMPARATIVE INCIDENCE OF TUBERCULOSIS IN DENTAL STUDENTS

A case-finding program similar to that carried out in the medical school has been in force at the Northwestern University Dental School for the past three years. The size of the classes in the Dental School averages about 75 students. The results of tuberculin tests and roentgen examinations are recorded in table 4. It is apparent that the rate of infection in the Dental School as shown by the tuberculin tests is very

much lower than in the Medical School. In the senior year, the average per cent of positive reactors is 69.1 as compared to 93.4 per cent in senior medical students. Of 205 roentgenograms made on freshman dental students, 27, or 13.2 per cent, showed calcareous deposits in the lungs or tracheobronchial lymph nodes and 4 students, or 1.9 per cent, had tuberculous lesions at or near the apex. Of 133 roentgen examinations of the chest in two graduating classes, 3 students, or 2.3 per cent, had tuberculous lesions. This is about half the incidence of lesions noted in seniors in the medical school. The above findings while limited in number suggest that the hazard of tuberculosis is greater among medical students than among students of dentistry.

COMMENTS ON PREVENTION AND DETECTION OF TUBERCULOSIS IN MEDICAL STUDENTS

From the information gained by this survey we feel that we shall be able to improve the program for the prevention and detection of tuberculosis in our medical students in the future. In a general lecture at the beginning of the junior year, it is planned to acquaint the students with the problem of tuberculosis as it affects them. A point to be stressed is the importance of obtaining sufficient rest. It is common for medical students to state that they have slept only five to six hours a night for weeks at a time. The sources of infection, such as the necropsy rooms, laboratories, patients and unsuspected tuberculosis in classmates, should be clearly outlined.

Strict sanitary precautions should be observed in the laboratories and necropsy rooms. Students should be instructed in and made to adhere to a strict aseptic technique in the examination of patients with known or suspected pulmonary tuberculosis. With the present tendency to make routine chest films on patients in general hospitals and clinics, the chances of the student being exposed to patients with unsuspected pulmonary disease will be lessened.

Because of the danger of cross-infection, every effort should be made to recognize early the presence of tuberculosis among students, faculty and employees of the medical school. Individuals with pulmonary lesions should not be allowed to continue with their routine work until sputa and gastric washings have been repeatedly negative for tubercle bacilli.

In order to reduce the mortality and morbidity of tuberculosis, early diagnosis is essential. The case-finding program as outlined by the Tuberculosis Committee of the American Student Health Association

is probably as thorough as is practicable in most institutions. This consists of tuberculin-testing of all first-year students with yearly roentgenograms of all reactors. Negative reactors are retested every six months and X-ray films made if and when the reactions become positive. By this procedure pulmonary lesions would be detected in their earliest stages.

As medical school administrators are now becoming aware of the problem of tuberculosis in their institutions and are adopting programs for its control, the incidence of the disease among medical students in the future should show a decrease.

SUMMARY

The tuberculosis case-finding program as employed at Northwestern University Medical School is outlined. The percentage of reactors to tuberculin in five classes increased from 66.2 per cent in the first year to 93.4 per cent in the fourth year. Roentgenological findings in the chest in eight classes in medical school are tabulated. Among 700 students in five classes who passed through the four-year medical course, clinical tuberculosis developed in 1 per cent and an additional 1.7 per cent developed latent pulmonary lesions. The course of the disease in these individuals is described. Factors considered to be of importance in its development were exposure to patients, cross-infection among students and overwork. Dental students had a lower incidence of tuberculous infection and pulmonary lesions than medical students. Comments are made on the prevention and early detection of tuberculosis in medical students.

The authors gratefully acknowledge the aid of Dr. James A. Britton who examined all of the students who developed tuberculosis and made decisions as to their treatment.

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REHABILITATION OF THE TUBERCULOUS[1,2]

LOUIS E. SILTZBACH

This paper on the rehabilitation of the tuberculous is further small evidence of our increasing awareness that this undeveloped facet of the antituberculosis campaign is one of the most pressing problems before us. The conviction is spreading that in order to give meaning and substance to our new slogan, "No more tuberculosis by 1960," we shall now have to direct a large portion of our energy and ingenuity toward the establishment of a thoroughgoing rehabilitation program with general application to our postsanitorium tuberculous population.

I find it helpful to think of a well balanced antituberculosis scheme as resting on a tripod. Historically, the first leg which we have used for support was—and is—the tuberculosis sanatorium and hospital. In these institutions we initiated and are perfecting the therapeutic techniques and skills used in bringing our patients back to health. But not so long ago we found that this one leg would not keep the whole structure stable. Our patients came to us for treatment, in most instances, much too late. So we built a second leg for our tripod: mass surveys and contact examinations to detect early cases. In the metropolitan area, the dynamic approach of Dr. Herbert R. Edwards and his staff has done much to strengthen that second leg. But still the antituberculosis structure is not secure; throwing our patients back into the unhealthful environment that produces their disease simply invites its resurgence and their readmission to the sanatorium. Thus we have come to recognize the need for a general rehabilitation program. And that, of course, completes our tripod.

But how frail that third leg is to-day! Only 1 to 4 per cent of patients discharged from sanatoria receive any vocational rehabilitation, whereas surveys tell us that about half the discharged patients need it. Terry C. Foster of the Vocational Rehabilitation Division of the United States

[1] From the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York, New York.

[2] Read before the meeting of the Tuberculosis Sanatorium Conference of Metropolitan New York, held at Montefiore Hospital January 15, 1941.

Office of Education told the 1940 National Tuberculosis Association Meeting at Cleveland that for years the Federal and State Rehabilitation Divisions have been loathe to come to grips with the problem of the discharged tuberculous, primarily because of the high percentage of breakdowns among them. Of course they were judging by breakdowns among patients discharged from sanatoria without benefit of rehabilitation. On the other hand, Mr. Foster found that excellent results were obtained with rehabilitated patients. He surveyed 400 such discharged patients. He found the results so impressive, when compared to the bleak outcome in the general run of discharged patients, that he now felt that the Federal and State Rehabilitation Divisions would attack the problem with greater courage and with immeasurably more enthusiasm.

I think we can say we have definitely passed the discussion stage of the rehabilitation problem. Of great interest locally is the joint project recently launched by the New York Tuberculosis and Health Association and the New York State Department of Education. They are studying the vocational needs of several sample groups of the tuberculous of this area with the object of working out a program to answer these needs. Finally, I should like to mention the establishment of a government-sponsored Rehabilitation Board in Britain as reported in the last issue to arrive of the British Journal of Tuberculosis. Britain, in this moment when she must realistically evaluate man-power and the costs of maintaining it, embarks upon a large-scale government rehabilitation program. Apparently the British experts know that such a program saves far more than it costs.

Rehabilitation is a complex subject. It is compounded of unequal parts of medicine, sociology, economics, industrial management and general administration. It requires the joined efforts of trained personnel in all these fields, for our endeavors are fundamentally directed at augmenting all those environmental factors which tend to keep the discharged patient on the credit side of the health ledger. To consolidate the physical gains made at the sanatorium and to encourage positive healthy attitudes, planned graduated work programs or other forms of vocational training, good food and shelter, an adjusted family situation, a measure of economic security, all these are needed. And through these we achieve a reduction of breakdowns and sanatorium readmissions to a point approaching the irreducible minimum.

We do not yet know which type or types of rehabilitation project will have the widest and most beneficial application to the tuberculous patients in the metropolitan area. However, I should like to say some-

thing about one type of organization with which I have been working for the past five years, and I will treat particularly its medical aspects. I refer to the Altro Work Shops, conducted for the past twenty-five years by the Committee for the Care of the Jewish Tuberculous of New York.

Altro is an urban workshop where garments are made for hospitals and other institutions under conditions which are carefully supervised, medically and industrially. Its main function is to provide graduated work for about 135 patients with arrested tuberculosis, patients who are unable to work full-time in general industry, and who offer prospects of eventual full rehabilitation. In addition it accepts a group of patients, never exceeding 10 per cent of the total, who require permanent sheltered employment. These patients can function and even become self-supporting under conditions such as prevail in this workshop.

Patients spend eight hours daily at the shop, but working hours are not permitted to exceed those prescribed by the staff physician. A nurse in full-time attendance supervises work and rest periods, and when she finds anything unusual in the patient's physical or mental condition, she refers him to a staff physician for examination. A large terrace with steamer chairs is used for rest periods in good weather. An indoor rest room serves during inclement weather. The patient and his family at home are supervised as a unit by medical case workers who are in most instances graduate nurses as well as trained social workers. Until the patient becomes self-supporting his earnings are supplemented by a subsidy based on the needs of his family.

The medical staff consists of four part-time physicians. Two physicians follow the Altro patients; one follows the familial contacts; and the other is a staff psychiatrist. In addition to the staff physicians a consulting medical staff is available for special problems in the field of tuberculous and nontuberculous disease. Free interchange of data is maintained with the various public pneumothorax and follow-up clinics, particularly with the Montefiore Hospital Clinic, and as far as possible duplication of work is avoided.

The majority of the Altro workers are patients who have been discharged from the Montefiore Hospital Country Sanatorium at Bedford Hills, and a close working arrangement exists among staff physician, social worker and sanatorium physician. However, patients are accepted from all institutions and are referred by voluntary and public agencies as well as by private physicians.

One of the most important aspects of the medical work is the selection

of patients. Is the patient ready for rehabilitation and does he hold out a good prospect of completing his rehabilitation successfully? With our incomplete knowledge regarding prognosis in tuberculosis we are compelled to operate in this field from a more or less empiric base. The problem of when to start the rehabilitation course is almost identical with the one the medical director of the sanatorium must face in deciding the most propitious moment for discharging the patient. Altro has adopted as a minimum requirement (except for the few permanently sheltered patients) the clinical status "arrested" as defined in the National Tuberculosis Association classification: that is, "Constitutional symptoms absent. Concentrated sputum or gastric contents negative for tubercle bacilli on smear. Lesions stationary and no evidence of pulmonary cavity. These conditions shall have existed for six months, the last two of which the patient has been taking one hour's walking exercise twice daily, or its equivalent." It is preferred that the negative sputum and the stability of the lesion shall have existed for nine months or a year, especially in patients who have undergone numerous collapse procedures and whose clinical course was attended by periodic stormy episodes. For effective rehabilitation work it becomes increasingly important that the sanatorium physician, the physician of the follow-up clinic and the rehabilitation physician come together and agree on a common criterion for judging the suitability of patients for a rehabilitation course.

There is still some confusion in this field of medical work. Time and again an apparently cured patient who either has lost his job or has been unable to find one is referred for rehabilitation simply because he needs economic assistance to tide him over his period of difficulty. Other patients are referred for rehabilitation with open pulmonary cavities which cannot be closed with available therapy. Still others come irreparably handicapped by long illness and consequent permanent total disability. The problem of the last two groups of patients parallels and is closely intertwined with the general problem of the care and institutionalization of the custodial case. We defeat our ends if we allow the rehabilitation project to become a repository for patients who, for diverse reasons, cannot be made fit to reënter and function in the main stream of our socio-economic life. The solution of their problem lies, I am sure, in other directions.

When the patient is accepted an attempt is made to judge the probable duration of his rehabilitation course. The only guide here is his past sanatorium history. Altro patients fall into three groups: those who

will probably require a short-term course of a year or less; those who likely will need a middle-term course of one to two and a half years; and those who will require an even longer course. The middle group is by far the most numerous. In the short-term group are found patients with resorbed pleurisy, the patients with early lesions which were never open and which have become stabilized on bed-rest (that is, minus-minus sputum cases). In the large middle-term group, are the successful cases following bed-rest, pneumothorax and thorocoplasty with moderately severe previous clinical course and with successful conversion (that is, plus-minus sputum cases). In the long-term group, the smallest, are the permanently sheltered patients with severe past histories, with diminished pulmonary reserve, and, in a few instances where home conditions allow it, patients who have not been rid of their positive sputum but whose general condition permits some work (that is, plus-plus sputum cases). This group division is by no means a hard and fast one. Not infrequently the patient's response to the work program necessitates a change in the original evaluation. But in general the grouping holds. Let us take a patient who is ready to work. He starts working three or four hours a day, and this is raised by one hour increments as he shows he can accomplish more without undue fatigue. Generally a slow increase of hours is practiced at the beginning of the course because it is found that the patient adapts himself more successfully under such a program. He is examined once monthly. In point of fact, I feel that all patients discharged from sanatoria, no matter what work they pursue, are best off when observed at monthly intervals for the first year, since it is during this period that a great many reactivations occur. Later the intervals are lengthened to two months and more. The examination includes fluoroscopy and sputum studies. An X-ray film is taken when indicated, at least once every six months. In the successfully rehabilitated case the admission X-ray film and the X-ray film at discharge from the course should be identical.

After the patient has successfully attained a full-time work schedule, his entire record is scrutinized, and, if it is satisfactory, discharge is recommended. But thereafter for life the patient is examined periodically, generally once a year.

Not always is the outcome of the rehabilitation course successful. The frequency of reactivation depends to some degree on the type of patient accepted. At the Altro Work Shop, we find 13.7 per cent of minimal cases, 39.7 per cent far advanced cases. At Otisville Sanatorium,

36.4 per cent are minimal cases and only 9 per cent are far advanced. It is to be expected that patients from Otisville as a group will fare better with rehabilitation than the usual Altro group. Yet, despite the latitude of its acceptance criteria, Altro statistics for the years 1925 to 1934 show that 80 per cent of its discharged patients are working and well six months to ten years after finishing their rehabilitation course.

These are very encouraging figures.

I am at present engaged in making a medical survey of approximately 1,000 patients who have passed through the Altro Work Shops in the last quarter century. I hope that this study will throw additional light on the question of reactivation of the disease process during the rehabilitation course as well as upon other related questions.

In the end, the rehabilitation project is the crucible wherein the validity of our therapeutic skills is definitively tested. Up to now, our therapies have hardly received a fair test of their enduring value. We have had to evaluate them in patients who are exposed to all the adverse effects of their unhealthful postsanatorium environment. From our rehabilitated patient only will we be able to judge the lasting merits of our medical therapy in pulmonary tuberculosis.

CLINICAL NOTES

EXTRAPLEURAL LOWER LOBE COLLAPSE DURING UPPER SELECTIVE THORACOPLASTY[1]

ARTHUR H. AUFSES

During the performance of a thoracoplasty for pulmonary tuberculosis, a pleural tear occasionally occurs because of the presence of an unsuspected free pleural space. Usually this space is localized and no untoward symptoms arise. If there are no pleural adhesions, complete collapse of the lung may ensue with marked respiratory distress. This complication is well known and the surgeon is prepared to combat it.

If the literature on the subject can be taken as a criterion, an extrapleural collapse of the lower lobe during an upper-stage thoracoplasty is an extremely rare occurrence. A careful search revealed only one case, reported by Judd (1) in 1938. It is possible that this complication is not as rare as it appears to be but is erroneously thought to be an intrapleural collapse. A number of years ago, during the removal of the third rib upon a patient who had had previous unsuccessful attempts at pneumothorax, a pleural tear occurred. There was complete collapse of the lung with such sudden respiratory distress that the patient had to be turned on the table so that the operated side was dependent. The wound was then packed with iodoform gauze and strapped, and the patient was returned to bed. He recovered and, after the pleural reaction had subsided, the lung reëxpanded and the wound healed. The second and first ribs were removed at a second operation, followed by uneventful recovery. During the third operation, while the sixth rib was being separated, there was again a collapse of the lower lobe and the operation had to be discontinued because of respiratory distress. It was felt that this was due to a tear into a free pleural space but it was very difficult to envision a free pleural cavity still being present after the previous complication. In retrospect, it is possible that the second pulmonary collapse was due to extrapleural separation of the lower lobe, similar to the case which is reported here.

H. W., # 12602, a twenty-five year old white male clerk, was admitted to Montefiore Sanatorium on August 28, 1939. His mother died from pulmonary tuberculosis when he was seven years old. He had been checked-up frequently during childhood and had been found negative. In 1933, he felt run down and had frequency, nocturia, occasional dysuria but no haematuria.

[1] From the Surgical Division and the Division of Pulmonary Diseases, Montefiore Hospital for Chronic Diseases, New York, New York.

No definite diagnosis was made. In 1935, he had some vague gastrointestinal symptoms and then was well until May, 1939, when he had cough, blood-streaked sputum and temperature of 102°F. X-ray examination in June showed an infiltration at the right apex, and his sputum was positive for tubercle bacilli. In June, 1939, pneumothorax was attempted unsuccessfully three times on the right side. He had been on bed-rest for two months before admission and had gained 25 pounds.

X-ray examination on admission showed a dense shadow in the right apex extending to about the level of the first interspace anteriorly, with a number of areas of decreased density. There were a number of calcific deposits in the upper portion of the hilar region at the level of the first interspace and second anterior rib. On the left there were a number of calcific deposits scattered between the level of the first and third anterior ribs.

X-ray examination on March 25, 1940 showed a cavity on the right side overlying the first rib. Pneumothorax was again attempted on two occasions but was unsuccessful. His sputum was consistently positive and he was transferred to Montefiore Hospital on May 15, 1940 for thoracoplasty.

The important features in the physical examination of this patient were his huge frame, with remarkably developed musculature, and weight of 201 pounds.

At the first stage, May 17, 1940, three ribs were removed, followed by an uneventful recovery. At the second stage, July 19, 1940, during the removal of the fifth rib, some difficulty in the anaesthesia occurred and the patient's respirations became very deep and forceful. Paradoxical motion was seen over the previously decostalized area. An assistant was instructed to exert pressure over this area to lessen the pulmonary excursion. Just as the fifth rib was removed, a loud sucking noise was heard and it was seen that the entire lung had collapsed against the mediastinum. At first it was thought that a pleural tear had occurred but on closer investigation it was found that the entire collapse had occurred in the extrapleural plane. The patient immediately gave evidence of respiratory distress and it was feared that removal of another rib would be dangerous. In order to steady the collapsed lung, the intercostal tissues attached to the lung surface were sutured to the tissues over the sixth rib, and the wound was closed in the usual manner. A needle was then inserted through a lower intercostal space in an attempt to remove any extrapleural air. None was found, and X-ray examination the following day showed that the lower lobe had reëxpanded and was in approximation to the chest wall. Following operation, the wound healed but the temperature remained elevated. Another X-ray examination showed fluid in the extrapleural space and this was drained through the lower angle of the wound. Some pus was evacuated and the temperature then returned to normal. The extrapleural infection rapidly subsided and the lung reëxpanded. Sputum became negative and the patient was returned to the Sanatorium for convalescence.

Judd offered no opinion as to the cause of the complication in his case. I believe that in the case reported here it was due to the paradoxical motion of the decostalized lung in a very muscular person who was experiencing respiratory difficulty during anaesthesia. During a deep inspiration of the lower intact thorax, with paradoxical motion of the upper lobe, there was an area along the next intact rib where a great force was exerted, tending to separate the lung from the bony thorax. This was probably enhanced by the assistant exerting pressure upon the operated area. During the performance of an extrapleural pneumonolysis, we have seen how easily the separation in the extrapleural plane may be made over the lower part of the lung. This is true even though the apex is firmly adherent to the chest wall. During thoracoplasty, once a small separation in the extrapleural plane has begun, exaggerated respiratory movements, plus a paradoxical motion of the already freed pulmonary tissue, might easily cause the remainder of the lung to strip away from the thoracic parietes.

SUMMARY

Extrapleural collapse occurring during thoracoplasty is an unusual complication and may be mistaken for intrapleural collapse due to an opening into a free pleural space. Treatment consists in fostering reëxpansion of the collapsed lung, as in intrapleural collapse.

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RECUMBENT POSTURE IN THE ELICITATION OF RÂLES[1]

RICHARD F. C. KEGEL

The relation of posture to the elicitation of râles has been noted by a number of observers. Among others, Cabot (1) stated: "If the patient lies on one side, râles, especially those of a moist variety, may become increased and intensified on the dependent side." Howard (2) noted that "râles which are associated with definite pathological changes are heard best, and sometimes exclusively, on the down side." The first observation in reference to tuberculosis apparently was made by Upham (3) in 1904: "In commencing phthisis, one can verify the presence of doubtful râles by the simple device of making the patient lie on the affected side." Ransom (4) likewise found that "in the early diagnosis of phthisis, adventitious sounds may be heard in the supine, while absent in the erect position," but to Flanagan (5) the procedure was of doubtful value.

The present study is an appraisal of posture in the elicitation of râles based on the examination of 101 patients, 25 men and 76 women, under treatment at the sanatorium. Their ages ranged between seventeen and forty-five. The large majority were under twenty-five years of age. The patients in this series presented, on X-ray examination, evidence of an early lesion confined to the upper third of the lung. Tubercle bacilli were found in the sputum or in the gastric contents in approximately 41 per cent of instances. In no case were râles elicited on repeated examination when the patient was in the upright position. However, when the patient assumed the recumbent position here described, persistent posttussic râles were heard over the site of the lesion as revealed by the X-ray in no less than 34 per cent of instances.

Moreover, the examination of another group of 45 patients presenting posttussic râles in the upright position disclosed that the distribution and the number of râles were greater when the patient was in the recumbent position. The examination of 25 healthy individuals in the recumbent position failed to reveal the presence of râles.

Posture: The patient is directed to lie on the affected side with the dependent shoulder depressed, the lower arm lying in front of and parallel to the thorax, and the upper arm placed above the head (figure 1). In this position the dependent half of the thorax is flexed, the upper half extended. Flexure of the dependent half of the thorax is important for the proper elicitation of the râles.

[1] From New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

The mechanism involved whereby the recumbent position favors the production of the posttussic râle is not understood. It is essential, for the proper

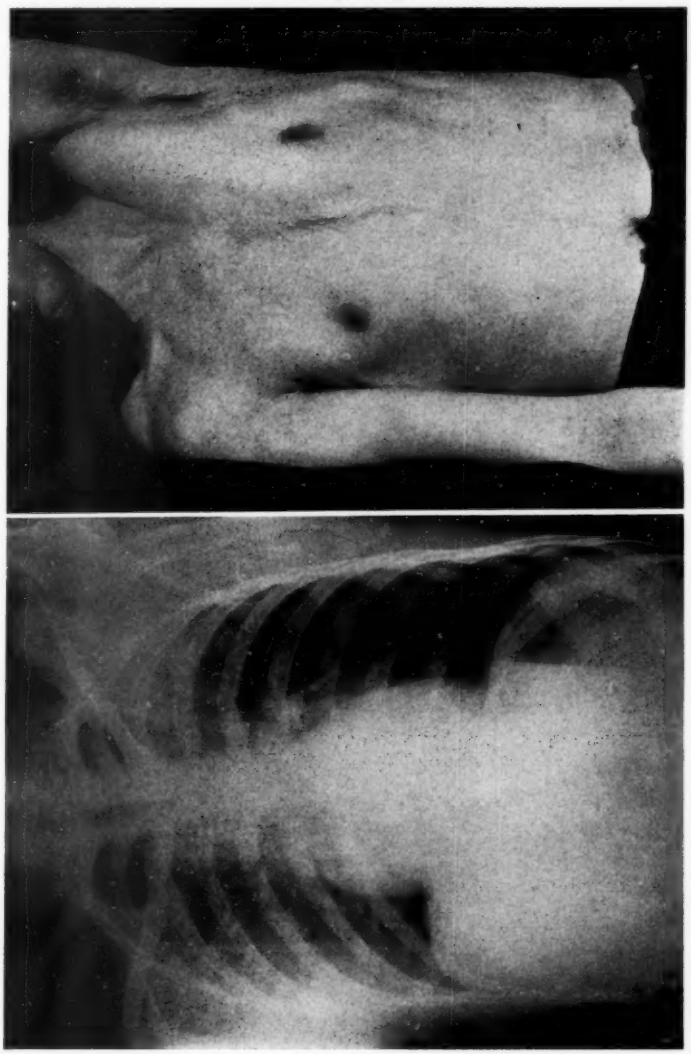

FIG. 1. Top. The recumbent posture
FIG. 2. Lower. Roentgenogram of the thorax following a full expiration

elicitation of the posttussic râle, that the air in the lung be fully depleted preceding the cough (6). The depletion of air in the affected lung is more marked in the recumbent than in the upright position (figure 2). It is probable that the

production of the posttussic râle is facilitated by this further depletion of air in the affected lung.

The present study indicates the importance of the recumbent posture in the elicitation of posttussic râles in the diagnosis of early pulmonary tuberculosis.

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SPONTANEOUS PNEUMOTHORAX[1]

A Method of Management

REEVE H. BETTS[2]

Spontaneous pneumothorax in the presence of a healthy contralateral lung is usually managed without difficulty. If the contralateral lung is grossly impaired, immediate relief may be a life-saving necessity of greatest urgency. Anyone engaged in collapse therapy for patients with pulmonary tuberculosis is frequently confronted with advanced bilateral disease. This may necessitate artificial pneumothorax on one or both sides, or frequently pneumothorax on one side and contralateral thoracoplasty. In any group of such cases spontaneous pneumothorax is an ever present possibility. It may occur at any time either spontaneously or following a refill of the pneumothorax space. Depending on the size of the bronchopleural communication and the status of the opposite lung, symptoms of mild to severe degree will be present. The milder cases may not necessitate treatment; others will subside with simple aspiration of the excess air on one or more occasions.

The severe cases with large bronchopleural leaks demand constant decompression. The method here described has been found by us to be very effective and quite satisfactory in dealing with such problems. The apparatus (figure 1) consists of a blunt, short beveled 16 or 17 gauge, two inch needle (A) which is inserted into the pneumothorax space. The needle is attached to a three-way Luer-Lok stopcock (B). After insertion, usually anteriorly or in the axilla, the needle and cock are securely fastened to the chest by means of adhesive strips. A Luer-Lok syringe (C) may be applied to the stopcock for immediate aspiration of air if necessary When the acute symptoms have been relieved, the other arm of the cock is attached to a piece of rubber tubing (D) about three feet long, and this in turn is connected with a glass connection (E) to another section of tubing long enough to reach a bottle placed under the bed. The tubing is in two sections in order to facilitate connection to the manometer of a pneumothorax apparatus (F) for pressure readings at desired intervals. The rubber tubing attaches to a glass tube (H) that is placed 1 cm. under water in the bottle (G). A second glass tube (I) only long enough to go through the rubber stopper is attached to a source of suction through connection with a second bottle (N) three-quarters full of water and fitted with a three-hole

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[2] 1101 Beacon Street, Brookline, Massachusetts.

stopper. The inlet and outlet tubes (K and M) are both short. A third piece of tubing (L) is placed under the water level from 3 to 6 inches. Suction is then applied and the amount of suction to be used is determined by the distance the long glass tube (L) is under water. Excess suction is neutralized by

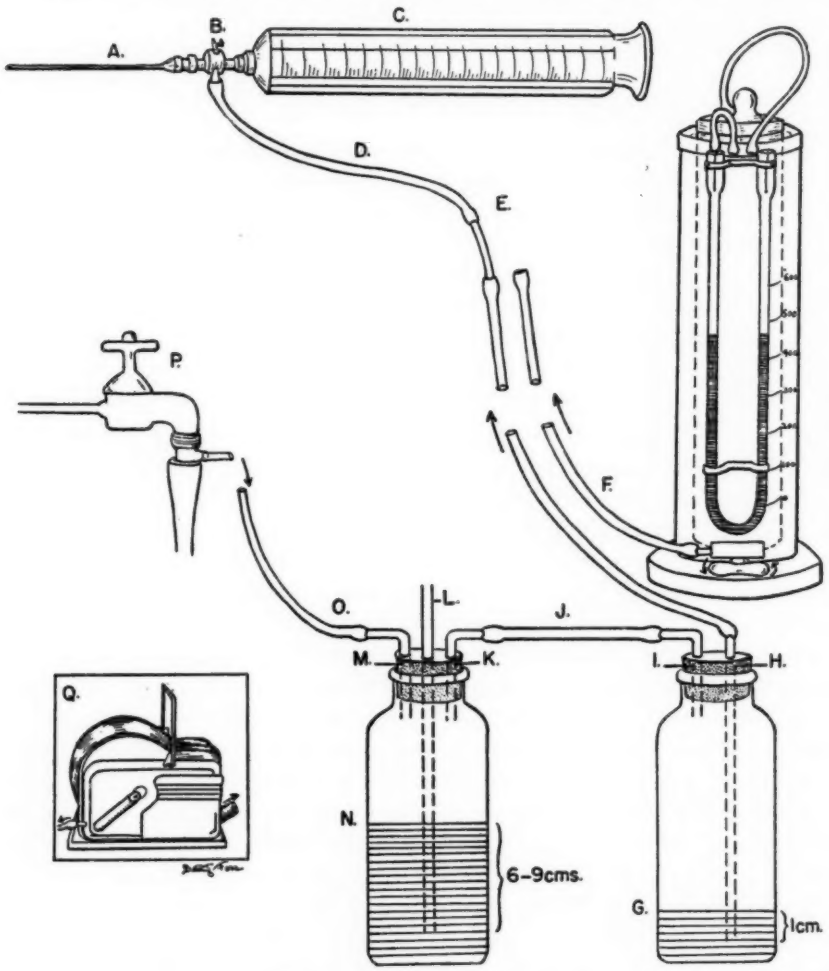

FIG. 1. See description in text

air entering the bottle through the open glass tube. The source of suction may be variable and as wall suction is not available in our hospital, either a water pump (P) or the silent Stedman magneto pump is utilized (Q).

This system provides constant gentle suction to the interior of the thorax. The amount of suction is adjusted by varying the distance the tube (L) is

under water. The amount of air that is withdrawn can be gauged by the bubbles escaping from the under-water end of tube (H). Should the system stop working, the needle can be tested by reapplying a syringe to the end of the stopcock (B) Manometer readings can be taken at any time.

Although most bronchopleural openings in such cases will close in twelve to twenty-four hours, the large and more dangerous ones may persist longer. We have used the above described apparatus in some cases that have necessitated leaving the needle in the thorax for as long as five days. With the use of sterile precautions in introducing the needle, intrapleural infection from extrinsic sources has not been encountered.

As a precautionary measure, a second sterile set-up of needle, stopcock and tubing is kept at the patient's bedside.

TUBERCULOSIS OF THE PAROTID GLAND[1]

P. J. SARMA

Tuberculosis of the parotid gland is rare. Nearly all contributions to the literature consist of single case reports. Because of its rarity, I am reporting this case with a follow-up of three and a half years. In 1932 Beerman and Fein (1) reviewed the literature and published, including their own case, much valuable information.

Tuberculous infection of the parotid gland may be haematogenous, lymphogenous or canalicular. The lymphogenous and haematogenous infections are difficult to differentiate on account of interlacing of the vessels. The haematogenous infection may be brought to the parotid from any primary focus in the body.

Lymphogenous infection may develop by way of the following sources:

1: Tuberculous infection of the tonsils. (The most frequent cause.)
2: Infection around the third molar may not only infect the parotid but also other salivary glands. Lymphatics from this location drain into the gland at the angle of the jaw following the retrograde stream.
3: In aural tuberculosis, infection may gain entrance from the external auditory canal through the lymph stream.
4: The lymphatics from the upper part of the nose and external two-thirds of the eyelid pass to the parotid lymph nodes, but no cases of tuberculosis from these locations have been reported.

CASE REPORT

Mrs. M. S., aged sixty-three, noticed a slight swelling in the region of left parotid gland in July, 1936. By September the swelling had continued to grow larger in size and was sensitive to touch.

The patient was first seen by me for this condition on October 7, 1936. At that time a firm mass, the size of a small orange, was felt in the left parotid region, extending from the lobe of the ear to the angle of the jaw. The skin in the centre of the mass was dark blue in appearance. On palpation the whole mass was firm and hard except over a small area (the size of a dime) which suggested some tumefaction. Pain was never a prominent symptom, but there

[1] From the Department of Surgery, University of Illinois College of Medicine, and Ravenswood Hospital, Chicago, Illinois.

was pain and limitation while opening and closing the mouth. The patient gave a history of using a strong antiseptic as a gargle, because of dryness and slight soreness of the throat.

The past history was negative, except that she had an epidermoid carcinoma of the chest wall which was removed by me on July 7, 1935, about thirteen months previously. The scar revealed no local recurrence. An X-ray film of the chest at this time was negative for metastases or tuberculosis.

Examination revealed general irritation of the oral mucosa, and two or three faint small ulcerative patches over the anterior pillars on both sides. The tonsils were normal. Bacteriological examination of the throat was negative. General physical examination did not reveal any abnormality. Blood studies, including Wassermann, were negative.

The patient was again seen in the latter part of November. At this time the swelling was not only larger but the skin in the centre had assumed the appearance of an ugly bruise. She complained of a great deal of pain. Blood examination revealed marked secondary anaemia. There was difficulty in swallowing solid food and because of this she had limited herself to a liquid diet. The patient was obliged to prop pillows behind her head when lying down to alleviate a choking sensation.

She now consented to an operation, which was performed on December 8, 1936. The preoperative diagnosis was carcinoma or a degenerative mixed tumor. Operation was performed under ethelyn-oxygen anaesthesia. A transverse incision with wide exposure was made. The tumor was removed with the discolored skin intact. An extensive dissection was made to remove all possible gland tissue. It was necessary to sacrifice a few fibres of the cervical facial nerve. Haemostasis was satisfactory. A small rubber tube drain was inserted and the wound closed with interrupted silk. Immediate postoperative condition of the patient was satisfactory.

Summary of pathological report by Dr. J. J. Moore: Marked chronic inflammatory reaction with hyalinized connective tissue and areas of necrosis around which are giant cells in the parotid gland. This is suggestive of tuberculosis (figures 1 and 2). No malignancy present. (Syphilis was ruled out by repeated blood tests.) Bacteriological examination of the material obtained from the necrosed areas of the gland was negative, while a guinea pig injected with the tissue developed tuberculosis.

A salivary fistula followed the operation but healed spontaneously within ten days. A slight drooping of the left lower lip was noticed. A roentgenogram of the chest, made two weeks after the operation, gave no suggestion of tuberculosis. Several X-ray treatments were given following the healing of the wound.

The patient has been examined at regular intervals including the last ex-

amination on July 8, 1940. At no time has any suggestion of a recurrence been noted. She is enjoying excellent health; the scar is not unsightly. A slight droop of the left lower lip remains. Her tongue is normal. No change in speech is noted.

Clinically, two types of tuberculosis of the parotid gland are recognized:

1: Acute inflammatory, which is diffuse and runs its course in a few days or weeks, ending in tumefaction, ulceration and multiple sinus formation.

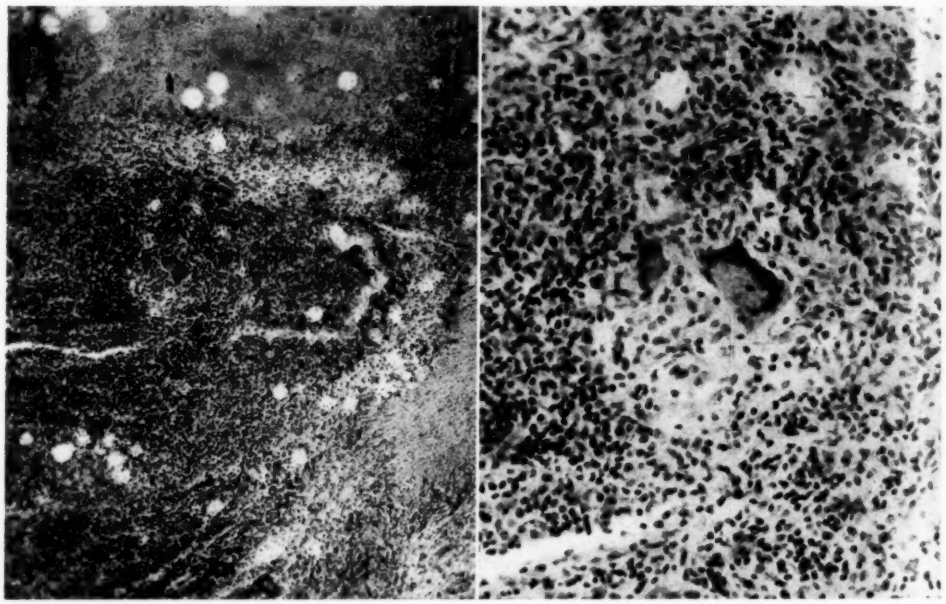

FIG. 1. Left. Caseous areas and giant cells. (Low power)
FIG. 2. Right. Epithelioid tubercle with giant cells. (High power)

2: Chronic or fibroid, which may run a chronic course without producing any symptoms for a long period.

The above mentioned case undoubtedly comes under the acute inflammatory type.

SUMMARY

A case of tuberculosis of the parotid gland is reported because of its rarity. Clinically it could not be differentiated from malignancy, mixed tumor or other inflammatory diseases.

Pathological examination of the surgically removed parotid gland revealed a marked chronic inflammatory reaction with hyalinized connective tissue and areas of necrosis around which giant cells were present. Bacteriological examination of the material obtained from the necrosed areas of the gland was negative, while animal inoculation revealed tuberculosis. A roentgenogram of the chest, made two weeks after operation, gave no suggestion of tuberculosis.

A salivary fistula followed the operation and healed spontaneously within ten days. Follow-up three and a half years after operation shows no recurrence.

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NOTICE

Starting with the next number of the American Review of Tuberculosis the Summaries of the original papers will be added in Spanish translation. It is hoped that this will increase the usefulness of the Review for our Latin-American colleagues and stimulate their interest in the work published in the Review. It should further strengthen the international ties of tuberculosis work.

The Review is greatly indebted to Dr. Arístides A. Moll, Secretary of the Pan American Sanitary Bureau, who has kindly consented to prepare or revise the Spanish translations.

AVISO

A partir del próximo número, los sumarios que acompañan a los trabajos originales publicados en la American Review of Tuberculosis aparecerán también en español. Espérase así acrecentar la utilidad de esta revista para los colegas de la América Latina, y atraer y avivar su interés en los artículos publicados en la misma, así como también ayudar a reforzar los lazos internacionales en tisiología.

Aprovechamos la ocasión para dejar constancia de nuestro agradecimiento al Dr. Arístides A. Moll, Secretario de la Oficina Sanitaria Panamericana, por su amabilidad en ofrecerse a preparar o revisar las traducciones al español.

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HEREDITY, CONSTITUTION AND TUBERCULOSIS

AN EXPERIMENTAL STUDY*

BY

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Edited by ESMOND R. LONG

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